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MEETING COVERAGE

CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

FROM THE 35TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, ATLANTA, GA; MAY 15-18, 1999

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

LUNG CANCER — PART I ETIOLOGY AND GLOBAL EPIDEMIOLOGY

Beginning with this issue, FUTURE ONCOLOGY will publish a series of articles on lung cancer that represent an update of a comprehensive review of this cancer presented in a previous issue (see FO pp 82-112).

GLOBAL EPIDEMIOLOGY

Lung cancer is the leading cause of cancer globally, affecting 1.1 million people (Exhibit 1). Incidence rates of lung cancer are higher in the developed world, and highest in the USA, Canada and Europe. Among the European countries, highest incidence rates are found in the UK, Hungary and Denmark.

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Although, based on worldwide incidence rates, lung cancer appears to be a disease of either affluence, or white race, or both, wide discrepancies in incidence rates may be artifactual rather than reflect an inherent lower predisposition for certain populations to develop lung cancer. Lung cancer is also a disease of old age which may explain why incidence rates of lung cancer are so much lower in the underdeveloped/developing world where life expectancy is generally shorter. However, such statistics may also be the result of inadequate recordkeeping stemming from failure to either diagnose lung cancer before death and/or fail to recognize it at death. Because lung cancer follows a rapid course after appearance of first symptoms, it may be mistaken for a respiratory infection, and noted as such on death certificates. However, if the low incidence reported in these regions isn't artifactual, it merits further study. It should be noted here that, in the USA, age-adjusted cancer incidence rates in blacks in the 1990 to 1996 period were 73.9 per 100,000 compared to only 27.6 per 100,000 among Hispanics. Therefore, it would appear that geography/environment may play a bigger role in this area than race. The influence of the environment in the incidence of lung cancer is highlighted by the fact that while the overall rate for American Indians/Alaska natives is low (29.7 per 100,000), a wide range in incidence rates is present by geographic area, from a low of 10.3 per 100,000 among American Indians in New Mexico, to a high of 76.4 per 100,000 among American Indians/Alaska natives in Alaska (Wingo PA, JNCI, 21 April 1999; 91(8), 675-690).

Lung cancer is mostly encountered in males who account for 73.6% of all cases worldwide. In certain regions where smoking is not prevalent among women, males account for nearly all lung cancer, as is the case in Southern Europe where males account for 86.6% of diagnosed disease. On the other hand, in the developed world where smoking is commonplace among women, the ratio is less pronounced, with males accounting for 69.7% of all cases in Northern Europe, and 54.8% in the USA.

Lung cancer is also the leading cause of cancer-related mortality globally, estimated to account for over 1 million deaths (Exhibit 5). Lung cancer is uniformly fatal, with overall USA 5-year survival rates of only 17.4%, under the most favorable diagnosis and treatment conditions.

TRIAD EPIDEMIOLOGY

Together, Canada, the USA, Europe and Japan, account for 56% of all reported cases of lung cancer, and lung cancer-related deaths (Exhibit 5). The high death rate illustrates the refractory nature of this cancer that does not respond to the most aggressive treatments.

Lung Cancer in the USA

Lung cancer claims 159,000 thousand lives in the USA, more than the combined toll of breast, prostate, and colorectal cancer. One of the most striking developments in this area is the rapid rise of the incidence and mortality attributable to lung cancer among American women. In 1999, the estimated 68,000 lung cancer deaths among women will exceed by at least 6,000 those attributable to breast and ovarian cancer combined.

In the USA, lung cancer is a disease of old age. According to SEER statistics, between 1992 and 1996, the age-adjusted incidence rate for lung cancer was 25 per 100,000 for those under 65 years-of-age and 348.6 per 100,000 for those >65 years-of-age. In this same period, age-specific incidence was under 31.7 per 100,000 in those <59 years-of-age, and 400.5 per 100,000 in those between the ages of 75 and 79 years-of-age. Perhaps the age bias in lung cancer is the reason that so little attention has been paid to this disease as compared to breast cancer. In 1998, funding for research in lung cancer was only $800 per each death attributable to this disease, compared to $7,500 for breast cancer, and a whopping $30,000 for HIV/AIDS research.

Despite the depressing statistics regarding the outcome of patients with this disease, there have been some good news. According to the second annual report to the nation on the progress in cancer prevention and control, prepared by the American Cancer Society, the National Cancer Institute (NCI), and the Centers for Disease Control and Prevention (CDC), and the National Center for Health Statistics (NCHS), that also included a special section on lung cancer and tobacco smoking, there was an average decline of 2.6%, in the age-adjusted incidence of lung cancer in males between 1990 and 1996. Age-specific incidence rates in males first declined at younger ages and then, for each older age group successively over time; rates in females appeared to be in the early stages of following the same pattern, with rates decreasing for women aged 40-59 years. Age-adjusted death rates among males also declined by an average of 1.6% per year.

Lung Cancer in Europe

Lung cancer is also common in Europe, particularly Northern Europe, where overall incidence rates per 100,000 match, and incidence rates per 100,000 in males exceed, those of the USA (Exhibit 3). High rates of lung cancer-associated mortality in such countries as Denmark and the rest of Scandinavia, and the UK (Exhibit 4), has prompted these countries to confront smoking as a serious health hazard. However, because smoking is widespread all over Europe, at least among males, variations in incidence rates may need to be examined closer to identify other factors that may contribute to such phenomena.

Lung Cancer in Japan

Overall, male and female incidence rates are significantly lower in Japan compared with other regions of the developed world (Exhibit 3). Nevertheless, between 1985 and 1989, according to the Research Group for Population-based Cancer Registration in Japan, lung cancer followed stomach cancer as the leading cause of cancer among males, but was ranked fifth among females in 1989 (Jpn J Clin Oncol, Jan 1998;28(1):54-67).

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Exhibit 1
Estimated Incidence of Lung Cancer Around the World by Gender in 1999

Country	Males (#)	Rate*	Females (#)	Rate*	Total (#)	Rate*	Male (%)	Total (%)
Eastern Europe	148,125	84.70	30,622	16.28	178,745	50.49	82.9	16.1
Northern Europe	41,943	90.05	18,251	37.70	60,191	63.88	69.7	5.4
Southern Europe	57,033	81.33	8,864	12.03	65,896	46.68	86.6	5.9
Western Europe	68,107	76.42	13,590	14.59	81,697	45.51	83.4	7.4
Europe, Total	315,208	83.30	71,327	17.78	386,529	49.59	81.5	34.8
China	172,393	27.37	69,232	11.70	241,625	19.54	71.3	21.8
Japan	33,374	54.18	12,468	19.44	45,842	36.81	72.8	4.1
Western Asia	16,799	18.28	3,179	3.66	19,978	10.97	84.1	1.8
South Eastern Asia	44,586	17.40	16,313	6.29	60,899	11.85	73.2	5.5
South Central Asia	55,297	7.46	12,521	1.79	67,818	4.63	81.5	6.1
Other Eastern Asia	9,712	25.37	4,005	10.36	13,717	17.87	70.8	1.2
Asia, Total	332,161	18.26	117,718	6.76	449,879	12.64	73.8	40.5
South America, Total	35,165	21.39	9,510	5.69	44,675	13.54	78.7	4.0
Central America	6,645	10.07	3,226	4.79	9,871	7.43	67.3	0.9
Americas, Total (excluding NA)	41,810	18.15	12,736	5.43	54,546	11.73	76.7	4.9
Canada	12,137	80.81	5,977	39.02	18,114	59.92	67.0	1.6
United States	93,994	71.76	77,594	56.65	171,588	64.21	54.8	15.5
North America, Total	106,129	72.69	83,577	54.88	189,706	63.79	55.9	17.1
Northern Africa	6,268	7.12	1,401	1.62	7,669	4.37	81.7	0.7
Western Africa	1,300	1.20	606	0.56	1,906	.88	68.2	0.2
Middle Africa	1,484	3.33	222	0.49	1,706	1.91	87.0	0.2
Eastern Africa	2,526	2.23	1,155	1.01	3,681	1.62	68.6	0.3
Southern Africa	4,385	18.10	1,388	5.61	5,773	11.86	76.0	0.5
Africa, Total	15,963	4.22	4,772	1.26	20,735	2.74	77.0	1.9
Australia/New Zealand	6,430	58.60	2,517	22.77	8,947	40.69	71.9	0.8
World, Total	817,701	27.59	292,647	10.03	1,110,342	18.88	73.6	100.0

**per 100,000 population*

Source: adapted from Ferlay J, etal, Globocan 1: Cancer Incidence and Mortality Worldwide, IARCPress: Lyon 1998 and Landis SH, etal, Cancer Statistics, 1999, CA Cancer J Clin, Jan/Feb 1999;49:8-31.

ETIOLOGY

Tobacco Smoking

Although exposure to tobacco smoke is considered the major risk factor for lung cancer, only about 11% of tobacco smokers ultimately develop lung cancer. Also, some data obtained from studies of populations with lung cancer are confusing. For instance, in a study performed in Turkey involving 1,046 patients diagnosed with lung cancer [966 were males (93%), and the remaining 80 (7%) were females], among males, 83% were current smokers, 12% were ex-smokers (abstained from smoking at least for 1 year), and the remaining 5% were non-smokers. In the female population, 16% were current smokers; 8% were ex-smokers, and 76% were non-smokers. The period of abstinence in the ex-smokers was 10 years or less in 77% of the patients. Among males, squamous cell carcinoma was the most common tumor type seen in the smokers (46%),

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while adenocarcinoma (45%) was the most commonly seen tumor in non-smokers. On the other hand, among female smokers, the most commonly noted tumor type was small cell lung cancer (54%), while among non-smokers it was adenocarcinoma (39%). In contrast to the findings of many other studies from developed countries, although the majority (83%) of male lung cancer cases were among smokers, the majority (76%) of female lung cancer cases were among non-smokers. Because only 80 female lung cancer patients were included in this study, these results may not be statistically significant but they may point to a separate etiology for lung cancer that is not linked to cigarette smoking. Such an etiology may generally be masked in the population studies involving males because of the widespread use of cigarette smoking among this group that makes it difficult to assess the impact of causes other than smoking in the development of lung cancer.

Exhibit 2
Estimated Mortality of Lung Cancer Around the World by Gender in 1999

Country	Males (#)	Rate*	Females (#)	Rate*	Total (#)	Rate*
Eastern Europe	130,327	74.67	24,245	12.92	154,571	43.80
Northern Europe	39,235	85.07	16,651	34.57	55,888	59.82
Southern Europe	52,480	74.83	8,512	11.56	60,990	43.20
Western Europe	65,910	73.97	13,224	14.20	79,137	44.09
Europe, Total	287,952	76.10	62,632	15.62	350,586	44.98
China	158,473	25.16	63,848	10.79	222,321	17.98
Japan	27,245	44.23	9,979	15.56	37,224	29.90
Western Asia	15,301	16.65	2,823	3.25	18,124	9.95
South Eastern Asia	41,024	16.01	15,016	5.79	56,040	10.90
South Central Asia	50,923	6.87	11,262	1.61	62,185	4.24
Other Eastern Asia	8,510	22.23	3,533	9.14	12,043	15.69
Asia, Total	301,476	16.57	106,461	6.12	407,937	11.46
South America, Total	28,523	17.35	8,223	4.92	36,746	11.14
Central America	6,012	9.11	2,687	3.99	8,699	6.55
Americas, Total (excluding NA)	34,535	14.99	10,910	4.65	45,445	9.78
Canada	10,379	69.11	4,642	30.30	15,021	49.71
United States	90,902	69.40	68,006	49.65	158,908	59.53
North America, Total	101,282	69.37	72,642	47.70	173,924	58.54
Northern Africa	5,757	6.54	1,288	1.49	7,045	4.02
Western Africa	1,192	1.10	552	0.51	1,744	.81
Middle Africa	1,363	3.06	204	0.45	1,567	1.76
Eastern Africa	2,163	1.91	983	0.86	3,146	1.39
Southern Africa	4,024	16.61	1,264	5.11	5,288	10.86
Africa, Total	14,499	3.83	4,291	1.13	18,790	2.48
Australia/New Zealand	5,761	52.50	2,184	19.76	7,945	36.13
World, Total	745,505	25.16	259,120	8.88	1,004,627	17.08

**per 100,000 population*

Source: adapted from Ferlay J, etal, Globocan 1: Cancer Incidence and Mortality Worldwide, IARCPress: Lyon 1998 and Landis SH, etal, Cancer Statistics, 1999, CA Cancer J Clin, Jan/Feb 1999;49:8-31.

In the developed world, it is widely believed that cigarette smoking is a serious health hazard, responsible as a contributing cause of many human diseases. The Seven Countries Study, that correlated cohort-specific and pooled smoking habits at baseline, between 1957 and 1964, among 12,763 men aged between 40 and 59 years, living in Europe, the USA, and Japan, concluded that cigarette smoking is harmful to health. However, universality of this conclusion remains controversial. Adjusted hazard ratios for all-causes death in smokers compared with never smokers, were 1.3 for smokers of <10 cigarettes per day, and 1.8 for smokers of ≥10 cigarettes per day. Hazard ratios were elevated for death attributable to coronary heart disease, all stroke, other arterial disease, lung cancer, other cancer, chronic obstructive pulmonary disease, and other disease in smokers as compared with never smokers. There were a few instances in which never smokers had a higher cause-specific death rate than smokers of ≥10 cigarettes per day, but these were attributed to random variation associated with low prevalence of never smokers, and multiple comparisons. Risk associated with cigarette smoking was independent of the cultural background of affected populations (Jacobs DR, etal, Arch Intern Med, 12 Apr 1999;159(7):733-40).

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The developing world is just beginning to assess the health risks of tobacco smoking. Investigators in Argentina where lung cancer is the first cause of mortality in men, and there are no restrictions on smoking, also found a strong association between smoking and lung cancer. Among 200 men with lung cancer and 397 hospital controls, the odds ratio was 8.5 for current smokers, and 5.3 for former smokers. Risk increased with duration of smoking, and with the number of cigarettes smoked per day with the attributable risk for smoking being 85%. Smokers of black tobacco and more than 24 cigarettes/day showed a risk of 12.9 compared to non-smokers, and of 15.5 for those with a smoking history of over 40 or more years duration. There were more cases of adenocarcinoma than squamous cell carcinoma (Matos E, Lung Cancer, Sep 1998;21(3):155-63).

The mechanism by which tobacco causes lung cancer, or any other disease for that matter, has not been adequately described. In lung cancer, tobacco smoke may interfere with the process of DNA repair. Although a complex process, carcinogenesis resulting from tobacco smoke exposure may involve activation of procarcinogens that lead to adduct formation and subsequent failure of DNA repair, which would normally remove these adducts. When DNA repair capacity among newly diagnosed lung cancer patients is compared to that of age-matched controls, significant differences between the two groups emerge. For instance, lymphocytes from lung cancer cases consistently exhibit higher levels of chromatid breaks compared to controls which indicates that DNA repair capacity influences risk for lung cancer (Amos CI, etal, Recent Results Cancer Res 1999;151:3-12).

Environmental Factors

Numerous environmental toxins or noxious inhalants may increase the risk of contracting lung cancer (see FO, p 84). However, no direct etiologic link has been established between such environmental factors and lung cancer. For instance, a second analysis of the largest epidemiological study of UK radiation workers, based on the National Registry for Radiation Workers (NRRW) in the UK, and including a cohort of 124,743 workers, revealed that overall levels of mortality were lower than those expected from national rates; the standardized mortality ratio for all causes was 82, increasing to 89 after adjusting for social class. This 'healthy worker effect' was particularly strong for lung cancer, and for some other smoking-related non-malignant diseases (Muirhead CR, J Radiol Prot, Mar 1999; 19(1):3-26).

Hereditary Factors

Although a definitive link between heredity and lung cancer has not been established, there are indications that heritable genetic factors may influence the risk for lung cancer among those who are exposed to carcinogens such as cigarette smoke. For instance, risk of lung cancer in relatives of affected individuals increases when smoking is taken into account, implicating a hereditary component.

However, high-penetrance genes are likely to explain only a small proportion of familial cases. The hypothesis of a hereditary component in lung cancer is supported by several epidemiologic and molecular epidemiologic studies. Epidemiologic studies show an approximately 14-fold increased risk for lung cancer among average tobacco smokers, and an approximately 2.5-fold increased risk attributable to a family history of lung cancer after controlling for tobacco smoke. Segregation analysis suggests that a rare autosomal dominant gene may explain susceptibility to early-onset lung cancer, but only a minority of lung cancer cases which include a family history can be explained based on these results. Therefore, it is believed that more common genetic variants or polymorphisms play a role in lung cancer risk (Amos CI, etal, *ibid*).

Interestingly, a hereditary component in lung cancer may not involve any genetic factors predisposing to carcinogenesis, but certain genetic factors predisposing to addiction to tobacco smoke. In this regard, smoking may be as heritable as alcohol consumption, with the magnitude of the genetic effects on smoking being at least as great as that on alcoholism (Hughes GR, Behav Ther 1986;17:335–45). Possibly, in some individuals, there may exist heritable molecular genetic components, involving either a few, or perhaps numerous genes, that predispose them to nicotine and alcohol dependence. Genetic factors predisposing individuals to addiction to tobacco may dramatically change the widely held current view that tobacco is inherently addictive to all who smoke. Just as alcohol, tobacco may only be addictive to a select group of individuals with a predisposition to addiction.

SPECIAL REVIEW

ONCOLOGY TRENDS PRODUCT MARKETS — PART I

Lead by the continuous strong growth of the taxanes (see FO, pp 1025-1039), and bolstered by the successful introduction of several other anticancer agents, the global market for oncology drugs and related products enjoyed a very successful year in 1998, as illustrated in Exhibit 6. Below is a status report of individual agents on the global and/or regional markets, or nearing commercialization, belonging to three classes of oncology drugs, platinum-based agents, topoisomerase I inhibitors and antifolates/thymidylate synthase inhibitors.

One major target indication of agents within these three categories is colorectal cancer. As it happens, in mid-1999, the National Cancer Institute began patient accrual of a phase III randomized clinical trial to compare oxaliplatin, irinotecan, and 5-FU/leucovorin, in various combinations, as first-line treatment of metastatic colorectal cancer. The trial (6C), which is being led by Michael O'Connell, MD, at the Mayo Clinic (Rochester, MN), is to

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enroll 1,700 patients who are to be followed for five years to establish recurrence rates of six separate treatment regimens:

- 5-FU/leucovorin monotherapy on days 1-5, every 4 weeks
- irinotecan and 5-FU/leucovorin, weekly, for 4 weeks, then 2 weeks rest
- irinotecan on day 1, then 5-FU/leucovorin on days 2-5, every 3 weeks
- oxaliplatin on day 1 and 5-FU/leucovorin on days 1-5, every 3 weeks
- oxaliplatin on day 1, and 5-FU/leucovorin, administered by continuous IV for 48 hours, every 2 weeks
- oxaliplatin plus irinotecan, every 3 weeks.

Agents within these three categories are also being developed for the treatment for nearly every solid tumor, and represent large global market opportunities.

PLATINUM-BASED ANTICANCER AGENTS

The market of commercially available platinum-based drugs, namely carboplatin and cisplatin, both produced by Bristol-Myers Squibb, was bolstered by their synergy with the taxanes, resulting in a combined worldwide revenue of $677 million, representing a gain of 11.5% over 1997 levels.

Platinum-based agents are the cornerstone of numerous combination regimens used in common cancers such as lung and ovarian cancer, and represent a curative treatment as a monotherapy in testicular cancer. These agents are being clinically evaluated in nearly all malignancies, and oxaliplatin, a new platinum-based drug, has been approved in colorectal cancer.

Despite aggressive research to identify novel platinum-based drugs, conducted over the past several decades, only one agent, oxaliplatin, has exhibited a sufficiently attractive clinical profile to enter the USA market. Lobaplatin, a transplatinum-based drug under development by Asta Medica (Frankfurt am Main, Germany), was approved in China for several cancer indications in 1998, including metastic breast cancer, sclc, and chronic myelogenous leukemia (CML). However, there is no indication that the drug is being filed elsewhere.

Many other such agents, created in the laboratory (see FO, pp 19-20), failed in the clinic. Generally, the problem with all platinum-based chemotherapeutics is serious side effects such as neurotoxicity, nephrotoxicity and myelosuppression. Often, agents designed to exhibit a more favorable side effects profile prove to be less effective. Several formulations of existing platinum-based drugs and novel agents in preclinical and clinical development are described in Exhibit 7. Also it appears that results with JM216, an oral cisplatin analog, that was in late stages of clinical development, have been disappointing. A new class of platinum-based agents, the trans-oriented compounds, may be the next targets of clinical investigation.

A different avenue in enhancing the value of existing platinum drugs such as cisplatin, is to introduce means of preventing resistance and adverse side effects. Three major mechanisms of resistance have been identified:

- reduced drug transport and accumulation
- enhanced intracellular detoxification through glutathione and/or metallothioneins (see FO, p 18).
- enhanced DNA removal (or tolerance) of platinum-DNA adducts and increased DNA adduct repair

Investigators are attempting to enhance the effectiveness of platinum-based agents by improving the performance of currently available platinum drugs and by creating novel analogs of these agents. Several approaches are also being tried to mitigate toxicities associated with platinum-based drugs. One such approach involves administration of amifostine (Ethyol; U. S. Bioscience), a chemoprotective that prevents nephrotoxicity, and various growth factors to prevent myelosuppression and anemia.

Cisplatin

The market of cisplatin (Platinol; Bristol-Myers Squibb) has been bolstered by its synergy with the taxanes, with worldwide sales posting a 31% rise to $42 million in the 1Q99, from comparable 1998 levels. Cisplatin's original USA patent #4310515, held by Bristol-Myers Squibb (BMS) expired on January 12, 1999. Another cisplatin patent, #5562925, obtained by Research Corporation Technologies (RCT; Tucson, AZ) in 1996, that seems to be based on a certain behavior of cisplatin solution when exposed to light, does not expire until May 2012.

Pharmachemie (Oradell, NJ) had filed an ANDA for generic cisplatin based on the original patent which was tentatively approved by the FDA in May 1997, and has since updated its application to recognize the RCT patent. American Pharmaceutical Partners (APP; Melrose Park, IL) filed an ANDA for generic cisplatin based on the RCT patent which has been approved by the FDA. As a result APP obtained a 180-day exclusivity on the drug. As of August 1999, APP was in litigation with BMS in the federal court in New Jersey regarding the 2012 cisplatin patent. Pharmachemie is also contesting APP's 180-day exclusivity claiming that they filed an ANDA first.

If the 1996 patent is upheld in court, BMS, based on a patent expiration date of 2012, would enjoy an unprecedented 33-year market exclusivity for cisplatin. Other companies with tentative FDA approval include Fujisawa (Deerfield, IL), obtained in July 1997, and Bedford Laboratories (Bedford, OH), obtained in December 1998. There are millions of dollars in royalties at stake for the patent holders. BMS also stands to lose revenue from cisplatin if a generic version is introduced in the USA market, and a less expensive platinum drug may also capture market away from carboplatin, a more expensive branded product addressing similar indications.

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Carboplatin

The market of carboplatin (Paraplatin; Bristol-Myers Squibb) has benefited even more dramatically than cisplatin, as demand for this type of drugs rose, and carboplatin was shown to be as affective as cisplatin with fewer serious side effects. Worldwide revenues were $149 million in the first quarter of 1999, up 16% from 1998 levels.

Oxaliplatin

Oxaliplatin (Eloxatin; Sanofi), a third generation platinum compound based on the 1,2-diaminocyclohexane carrier ligand, lacks the nephrotoxicity of cisplatin and the myelosuppression of carboplatin. It is also effective *in vitro* in cell lines with acquired cisplatin resistance, and was shown to be clinically active in tumors intrinsically resistant to cisplatin (see FO, pp 810-811).

Oxaliplatin entered the market in France in 1996 as second-line therapy for advanced colorectal cancer, in combination with 5-FU and leucovorin, and moved to first-line therapy in May 1998. As of mid-1999, in addition to France, oxaliplatin was approved as first-line treatment, in combination with 5-FU and leucovorin, in eight European countries, namely Belgium, Germany, Italy, Luxembourg, the Netherlands, Spain, Sweden and the UK. Overseas sales in the first half of 1999 were approximately $33.3 million, up 88% from the comparable 1998 period.

In April 1999, Sanofi, now Sanofi-Synthelabo, entered into a joint venture agreement with Eli Lilly to codevelop and comarket oxaliplatin in the USA for colorectal cancer. Eli Lilly will provide initial capital-

Exhibit 3
Lung Cancer Incidence in Europe by Country and Gender in 1999

Country	Males (#)	Rate*	Females (#)	Rate*	Total (#)	Rate*
Belarus	3,652	74.32	560	10.14	4,212	40.35
Bulgaria	3,096	77.06	607	14.38	3,703	44.94
Czech Republic	4,929	98.40	886	16.74	5,814	56.46
Hungary	5,691	116.29	1,544	28.92	7,235	70.70
Moldova	1,161	54.38	283	12.08	1,443	32.25
Poland	16,285	86.73	3,406	17.17	19,691	50.99
Romania	6,994	63.61	1,506	12.93	8,500	37.54
Russia	58,658	84.77	12,619	16.02	71,277	48.16
Slovakia	2,246	85.60	343	12.40	2,589	48.06
Ukraine	45,413	89.60	8,868	17.50	54,281	53.55
Eastern Europe	148,125	84.70	30,622	16.28	178,745	50.49
Denmark	2,161	82.47	1,139	42.43	3,300	62.20
Estonia	591	87.82	113	14.61	704	48.72
Finland	1,813	72.41	400	15.19	2,213	43.08
Iceland	50	36.72	46	34.40	96	35.56
Ireland	1,179	65.52	546	29.97	1,724	47.64
Latvia	875	77.88	169	12.82	1,043	42.80
Lithuania	1,395	81.50	264	13.72	1,659	45.64
Norway	1,199	55.10	485	21.81	1,684	38.28
Sweden	1,860	42.47	900	20.06	2,760	31.14
United Kingdom	30,820	106.48	14,189	47.25	45,008	76.32
Northern Europe	41,943	90.05	18,251	37.70	60,191	63.88
Albania	806	50.53	146	8.42	952	28.60
Bosnia and Herzegovina	1,088	66.31	198	11.47	1,286	38.21
Croatia	2,104	92.87	383	15.90	2,486	53.22
Greece	4,534	86.38	749	13.95	5,283	49.76
Italy	26,515	96.14	4,466	15.27	30,981	54.51
Macedonia	542	53.93	88	8.76	630	31.36
Malta	103	55.11	10	5.00	113	29.84
Portugal	1,928	40.33	429	8.32	2,357	23.73
Slovenia	751	78.52	150	14.76	901	45.70
Spain	13,720	71.79	1,373	6.87	15,093	38.59
Yugoslavia	4,942	88.64	872	15.49	5,814	51.88
Southern Europe	57,033	81.33	8,864	12.03	65,896	46.68
Austria	2,886	72.88	939	22.51	3,826	47.04
Belgium	5,782	116.13	770	14.85	6,552	64.46
France	19,585	68.53	2,876	9.58	22,460	38.32
Germany	29,258	73.01	6,914	16.46	36,172	44.07
Luxembourg	190	91.30	36	17.01	226	53.70
Netherlands	7,706	99.46	1,475	18.67	9,181	58.67
Switzerland	2,700	75.52	580	15.83	3,280	45.30
Western Europe	68,107	76.42	13,590	14.59	81,697	45.51
Europe, Total	315,208	83.30	71,327	17.78	386,529	49.59

**per 100,000 population*

Source: adapted from Ferlay J, etal, Globocan 1: Cancer Incidence and Mortality Worldwide, IARCPress: Lyon 1998

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ization for the joint venture, and make upfront, and milestone payments based on regulatory milestones, and both companies will share future development costs. In August 1999, Eli Lilly filed an NDA for oxaliplatin, in combination with 5-FU/leucovorin, as first-line treatment of advanced colorectal cancer.

Oxaliplatin is being evaluated in a variety of solid tumors, including ovarian cancer, and mesothelioma, alone or in combination with other chemotherapeutics, including taxanes, topo I inhibitors and antifolates. Toxicities associated with oxaliplatin involve gastrointestinal events, such as diarrhea and vomiting, peripheral sensory neuropathy, and bone marrow toxicity; in comparison with the 5-FU/leucovorin regimen, diarrhea was seen in 12% versus 2%, vomiting in 7% versus 1%, and stomatitis in 6% versus 0%. The dose-limiting toxicity of oxaliplatin treatment appears to be neurological. Severe sensory neuropathy with functional impairment was encountered in 13%-16% of patients treated with the bimonthly combination of oxaliplatin and 5-FU/leucovorin.

TOPOISOMERASE I INHIBITORS

The market for topoisomerase I (topo I) inhibitors expanded rapidly in 1998, with worldwide sales reaching $364.9 million. For a comprehensive review of topo I inhibitors, see FO, pp 528-544 and 797-801.

Numerous research groups are attempting to elucidate the anticancer mechanism of topo I inhibitors in order to develop novel analogs of camptothecin, and related

Exhibit 4
Lung Cancer Deaths by Gender in Europe by Country in 1999

Country	Males (#)	Rate*	Females (#)	Rate*	Total (#)	Rate*
Belarus	2,965	60.33	393	7.12	3,358	32.17
Bulgaria	2,348	58.44	443	10.49	2,791	33.87
Czech Republic	4,874	97.30	866	16.36	5,739	55.73
Hungary	5,238	107.05	1,448	27.12	6,686	65.35
Moldova	896	41.97	212	9.06	1,108	24.76
Poland	14,629	77.91	2,811	14.17	17,441	45.16
Romania	5,234	47.60	1,089	9.35	6,323	27.92
Russia	52,793	76.29	9,815	12.46	62,607	42.31
Slovakia	1,931	73.58	281	10.17	2,212	41.05
Ukraine	39,419	77.77	6,887	13.59	46,306	45.68
Eastern Europe	130,327	74.67	24,245	12.92	154,571	43.80
Denmark	2,209	84.33	1,137	42.35	3,346	63.08
Estonia	543	80.65	98	12.69	641	44.36
Finland	1,646	65.76	345	13.09	1,991	38.76
Iceland	46	34.38	46	34.40	93	34.39
Ireland	1,084	60.26	500	27.46	1,584	43.77
Latvia	696	61.95	123	9.32	818	33.57
Lithuania	1,201	70.12	195	10.14	1,396	38.38
Norway	1,088	50.00	412	18.55	1,501	34.11
Sweden	1,911	43.63	920	20.53	2,832	31.94
United Kingdom	28,811	99.54	12,875	42.88	41,686	70.69
Northern Europe	39,235	85.07	16,651	34.57	55,888	59.82
Albania	709	44.43	128	7.36	837	25.12
Bosnia and Herzegovina	945	57.57	170	9.86	1,115	33.13
Croatia	1,871	82.58	331	13.76	2,202	47.13
Greece	4,266	81.27	747	13.91	5,012	47.21
Italy	24,587	89.16	4,341	14.84	28,928	50.90
Macedonia	493	49.08	85	8.46	578	28.79
Malta	100	53.41	15	7.78	115	30.40
Portugal	1,832	38.32	420	8.15	2,251	22.67
Slovenia	687	71.86	141	13.85	828	42.00
Spain	12,654	66.21	1,332	6.66	13,986	35.76
Yugoslavia	4,336	77.78	802	14.24	5,138	45.85
Southern Europe	52,480	74.83	8,512	11.56	60,990	43.20
Austria	2,509	63.34	807	19.35	3,316	40.78
Belgium	5,774	115.98	771	14.87	6,546	64.39
France	18,924	66.22	2,839	9.45	21,763	37.13
Germany	28,714	71.65	6,947	16.54	35,661	43.45
Luxembourg	176	84.78	34	15.98	210	49.96
Netherlands	7,433	95.94	1,335	16.90	8,769	56.03
Switzerland	2,380	66.59	491	13.40	2,872	39.66
Western Europe	65,910	73.97	13,224	14.20	79,137	44.09
Europe, Total	287,952	76.10	62,632	15.62	350,586	44.98

**per 100,000 population*

Source: adapted from Ferlay J, etal, Globocan 1: Cancer Incidence and Mortality Worldwide, IARCPress: Lyon 1998

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agents (Exhibit 8). It is believed that camptothecin and indolocarbazoles recognize identical structural elements of the topoisomerase I-DNA covalent complex, but differ in terms of sequence-specificity of topo I-mediated DNA cleavage. It was currently shown that topo I is a dual enzyme with a DNA cleavage site juxtaposed to a functionally independent kinase site. Therefore, indolocarbazole drugs can inhibit both the DNA cleavage/religation and kinase activities of this enzyme (Labourier E, etal, Cancer Research, 1 January 1999;59:52-55). Also, one area of intense activity is reformulation of camptothecin in liposomes. Because camptothecin undergoes rapid hydrolysis at physiological pH, forming biologically inactive carboxylate species, encapsulation in liposomes is expected to increase its effectiveness.

Topo I inhibitors such as topotecan and irinotecan also appear to cross the blood-brain barrier (BBB), and have demonstrated activity against intracranial malignant brain tumors. In animal models, topotecan labeled with a radioactive tracer, readily entered intracranial tumors. Also, measurable concentrations of the drug remained two hours following administration. During this period, drug concentrations within contralateral normal brain were never reproducibly greater than background, suggesting that systemically administered topotecan enters malignant brain tumors with disrupted BBBs and, therefore, may be useful in the treatment of sensitive intracranial tumors (Lesser GJ, etal, ASCO99, Abs. 568:148a).

Currently approved topo I inhibitors are administered intravenously. However, there are various orally available topo I inhibitors under development (Exhibit 8). Oral versions of both irinotecan and topotecan (see below) are in development, as is 9-nitro-20-(S)-camptothecin (9-NC, RFS2000, Rubitecan), a patented analog of camptothecin developed at the Stehlin Foundation for Cancer Research (Houston, TX), in collaboration with SuperGen (San Ramon, CA). RFS2000 is 2 to 3 times more active *in vitro* than camptothecin. RFS2000 is being evaluated, as monotherapy or in combination with other drugs, in a variety of tumor types, in ongoing phase II clinical trials in the USA and in Europe. Tumors targeted include colorectal, gastric, lung, breast, head and neck, and prostate cancer, and leukemia. According to phase I clinical trials, a dose of 1.5 mg/m^2 daily, for 5 days, every week, was well tolerated as prolonged administration in chemotherapy-naive or moderately pretreated patients. Dose-limiting toxicity was myelosuppression, and prolonged administration resulted in mild to moderate chemical cystitis in approximately 20% of patients. There was no other significant toxicity.

According to preliminary results from a phase II clinical trial, in untreated or moderately pretreated pancreatic cancer, approximately 50% of evaluated patients achieved a significant subjective benefit, with approximately 10% achieving a major objective response. Median survival for untreated patients was over 7 months, which compares favorably with that achieved with the 5-FU and gemcitabine combination regimen. Confirmatory phase II studies in pancreatic cancer are ongoing, and randomized studies have been initiated comparing RFS2000 to gemcitabine, in untreated patients, and to 5-FU, in those refractory to gemcitabine.

In a phase II clinical trial of RFS2000 in heavily pretreated ovarian cancer refractory to platinum and taxanes, a PR rate of 8% was observed with an additional 16% of patients experiencing a serologic response, and 50% prolonged stabilization of disease (L Lenaz, etal, 9nth Conference on DNA Topoisomerases in Therapy, 5-7 Oct 1998, Abs. 26).

RFS2000 has also demonstrated activity in hematologic cancer. In a pilot clinical trial, patients with CMML (n=4) and Ph-negative CML (n=6) were treated with RFS2000 (2 mg/m^2), daily, for 5 days, every week. Dose was adjusted according to myelosuppression and toxicity. Treatment lasted a median of 34.5 weeks (range=6-120+). There were 4 minor responses and 6 PR or CR (Kantarjian H, etal, ASCO99, Abs. 83:23a).

However, in July 1999, Idec Pharmaceutical (San Diego, CA) discontinued development of 9-aminocamptothecin (9-AC), a water-soluble, orally available camptothecin analog that was being evaluated in phase II clinical trials in 8 tumor types including ovarian, brain, lung and kidney cancer.

Topotecan

Worldwide sales of topotecan (Hycamtin; SmithKline Beecham) were about $32.0 million, in the first quarter of 1999, up 24% from the comparable 1998 quarter. Worldwide sales were $36.8 million in the second quarter of 1999, up 33% from the comparable 1998 quarter, bringing six-month 1999 worldwide sales to about $68.8 million, up 29% from the comparable 1998 period.

Hycamtin, was originally approved in the USA on May 28, 1996 as an IV treatment for metastatic ovarian cancer after failure of first-line chemotherapy. Subsequently, on November 30, 1998, Hycamtin was also approved in the treatment of chemotherapy-sensitive (defined as disease responding to chemotherapy, but subsequently progressing at least 60-90 days after chemotherapy) small cell lung cancer (sclc) after failure of first-line chemotherapy.

Based on 1998 USA sales of $76.8 million and an average wholesale price (AWP) of $575.20 per 4 mg of Hycamtin, the cost for one treatment cycle was $1,941.30 and the cost of a single regimen was $9,706.50, assuming that an average of 5 cycles were delivered. Based on these numbers, approximately 8,000 patients were treated with Hycamtin in the USA in 1998.

An oral formulation of topotecan is also undergoing clinical evaluation in ovarian cancer and sclc. In a phase II clinical trial, conducted by the Topotecan Study Group, oral topotecan was administered as a single agent, second-line therapy in platinum-refractory advanced (Stage III/IV)

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epithelial ovarian cancer. Topotecan (2.3 mg/m^2) was administered daily, for 5 days, every 3 weeks, to 116 patients. The overall response rate was 18.1% with 3 CR (2.6%) and 18 PR (15.5%); disease stabilized in 28 (24.1%) and progressed in 49 (42.2%) patients. Median time to progression was 15.1 weeks, and median survival had not been reached at the time results were presented, at a median follow-up of 32.1 weeks. Hematologic toxicities by course included Grade 4 neutropenia (15.3%), Grade 3/4 anemia (7.2%/1.8%), and Grade 4 thrombocytopenia (6.2%). The most frequently occurring non-hematologic toxicities by course were mostly low grade alopecia (53.4%), nausea (40.9%), vomiting (14.3%), fatigue (23.8%), and diarrhea (19.4%). This preliminary analysis suggests that orally administered topotecan, on this schedule, may be as active as IV topotecan, as second-line therapy in advanced epithelial ovarian cancer with less Grade 4 neutropenia (Clarke-Pearson DL, etal, ASCO99, Abs. 1421:368a).

A multicenter randomized phase II clinical trial, being conducted by the European SCLC Topotecan Study Group, is comparing oral topotecan (2.3 mg/m^2) with IV topotecan (1.5 mg/m^2), both administered on days 1-5, every 21 days, as second-line therapy of sensitive (recurrent) sclc, 3 months after cessation of initial chemotherapy. Among 106 patients (PO=52, IV=54), stratified according to duration of response to prior chemotherapy, staging (limited or extensive disease) and presence or absence of liver metastases, there were 12/52 (23.1%) responses in the PO arm, consisting of 1 CR and 11 PR, and 8/54 (14.8%) responses in the IV arm, consisting of 2 CR and 6 PR. At the time of this analysis median time to progression was 14.9 weeks in the PO arm, and 13.1 weeks in the IV arm, with median survival of 31.4 weeks and 25.7 weeks, respectively. Regarding adverse events, Grade 4 anemia was equivalent at 1% in both arms, with comparable rates of thrombocytopenia (PO=9.4% and IV=7.3%); Grade 3/4 neutropenia was lower in the PO arm (Grade 3=25.1% and Grade 4=12.8%) compared to the IV arm (Grade 3=38.9% and Grade 4=34.0%). The rate of Grade 3 nausea and vomiting was similar in the two groups and no Grade 4 vomiting or diarrhea was reported in either arm (Pawel JV, etal, ASCO99, Abs. 1816:471a).

Similarly, in a phase II clinical trial, oral topotecan was well tolerated in untreated advanced nsclc, resulting in useful symptom palliation, and a 10-month median survival. Thirty patients with nonresectable Stage III/IV nsclc were treated for 5 days, every 21 days, with daily oral topotecan (2.3 mg/m^2) for the first cycle, and with modified subsequent doses according to tolerability; dose escalation to 2.7 mg/m^2 for 5 days was possible in 83% of patients. Among 27 assessable patients, there were 3 (11%) minor responses, and disease stabilized in 10 (37%). Median survival was 10.2 months. Myelosuppression was the major toxicity with 12 (40%) patients experiencing Grade 3, and 2 (6.6%) Grade 4 neutropenia. Other hematologic adverse events included Grade 3/4 anemia, occurring in 3 and 1 patient, respectively. There was one episode of Grade 3 thrombocytopenia. The main non-hematological toxicities consisted of Grade 3 nausea (13%) and vomiting (13%). Regarding symptom palliation, 21% of patients experienced improvement in dyspnea, 32% in cough, and 29% in fatigue (White SC, etal, ASCO99, Abs. 2033:527a).

Irinotecan

Irinotecan (CPT-11, Camptosar; Pharmacia & Upjohn and Campto; Aventis) amassed worldwide sales of $246.3 million in 1998. Worldwide sales of Camptosar (North and South America) were $129 million in the first half of 1999, up 51% from 1998 levels. Camptosar was approved in June 1996 for treatment of metastatic carcinoma of the colon or rectum which has progressed or recurred after treatment with 5-FU. Pharmacia & Upjohn is planning to file an sNDA for Camptosar as first-line therapy of advanced colorectal cancer in late 1999 based on favorable results from recently completed clinical trials.

Based on an AWP price of $185.44 for 40 mg/ml of Camptosar, the cost per cycle was $4,174 in 1998, resulting in a cost per regimen of $14,603. Based on results from phase II clinical trials, 3.5 cycles were delivered bringing the cost per regimen to $14,603. Approximately 11,000 patients were treated with Camptosar in the USA in 1998.

Worldwide sales of Campto, outside North and South America and Japan, were $41.6 million in the first half of 1999, up 116% from 1998 levels. As of mid-1999, Campto was approved as first-line treatment for advanced colorectal cancer, in combination with 5-FU and leucovorin, in all EU markets except Spain where it was filed and awaiting approval.

THYMIDYLATE SYNTHASE INHIBITORS/ANTIFOLATES AND RELATED AGENTS

Inhibition of thymidylate synthase (TS) by the combination of 5-FU and leucovorin has been marginally effective in the treatment of advanced colorectal cancer. A major limiting factor with this therapy is that its effectiveness depends upon delivery of adequate concentrations of 5-FU and leucovorin to the tumor cells, and on the anabolism of 5-FU to 5FdUMP and the intracellular conversion of leucovorin to 5,10 methylene tetrahydrofolate. These key steps are influenced by the biochemical profile of tumor cells, and the clearance of these drugs by the patient. To circumvent these limitations, investigators have designed novel TS inhibitors that bind to the reduced folate binding site of TS, and act independent of any cofactor (Erlichman C, ASCO95 Educational Book). Despite these attempts, TS inhibitors and related agents still remain investigational, with only one, capecitabine, approved in the USA, and four, UFT, raltitrexed, doxifluridine (Furtulon; Roche), launched in Japan in 1987, and carmofur, launched also in Japan in 1981, being marketed abroad.

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Capecitabine

Capecitabine (Xeloda; Roche), an orally available 5-FU prodrug, is a tumor-selective fluoropyrimidine (see FO pp 806-808) that was approved in the USA in April 1998 as third-line treatment of metastatic breast cancer, refractory to both paclitaxel and an anthracycline-based regimen. Because tumor-selective enzymatic activation of capecitabine by thymidine phosphorylase results in higher concentrations of 5-FU within tumors compared to plasma and normal tissues, this drug may be applicable in cancer indications presently addressed by 5-FU. One such indication is colorectal cancer for which an sNDA was filed in September 1999.

The efficacy and safety of capecitabine in the treatment of advanced metastatic colorectal cancer was compared to the standard regimen of 5-FU biomodulated with leucovorin (Mayo regimen) in an open label, randomized phase III trial that enrolled 605 patients from the USA, Canada, Brazil and Mexico. Of these, 302 were randomized to capecitabine (2500 mg/m^2), administered daily for 14 days, every 3 weeks, and 303 to 5-FU (450 mg/m^2) and leucovorin (20 mg/m^2) infused on days 1-5, every 4 weeks. The overall best response rates were 23.2% (1.3% CR) and 15.5% (1.0% CR) in the capecitabine and Mayo arms, respectively. Duration of response of 9.1 versus 9.7 months, and progression-free survival of 4.4 versus 5.1 months, were similar in both treatment arms. Serious adverse events occurred in 13.4% of patients treated with capecitabine versus 23.1% in the 5-FU/leucovorin group. The most common toxicities of capecitabine were Grade 3 hand-foot syndrome (17.7%), and Grade 3/4 diarrhea (15.1%) while the most common Grade 3/4 toxicities of the Mayo regimen were neutropenia (25.9%), stomatitis (16.3%), and diarrhea (13.9%). Dose reductions were instituted in 40% and 45% of patients, respectively. Oral administration of capecitabine resulted in a higher response rate and a more favorable toxicity profile than the IV 5-FU/leucovorin regimen (Cox JV, etal, ASCO99, Abs. 1016:265a).

Raltitrexed

Raltitrexed (Tomudex; AstraZeneca) has been approved for treatment of metastatic colorectal cancer in certain European markets. However, despite a hefty 50% increase in the first half of 1999, compared to the same 1998 period, worldwide sales of raltitrexed were only $12 million. One of the problems faced by raltitrexed is that it has not obtained FDA approval to enter the USA market (see FO, pp 811 and 481). This drug faces a tough competitive environment as monotherapy in advanced colorectal cancer but may find a place as part of combination regimens.

A multicenter, 57-patient, phase II clinical trial was initiated in June 1998 in France, to evaluate a combination regimen of raltitrexed (3 mg/m^2), administered as a 15-min infusion, followed 45 minutes later by oxalipatin (130 mg/m^2), administered as 2-hour infusion, repeated every 3 weeks, as first-line chemotherapy of metastatic colorectal cancer. In an interim analysis, among 20 patients evaluable for efficacy, there were 8 (40%) PR, and disease stabilized in 10 (50%), and progressed in 2 (10%). Median response duration had not been reached at the time of this report but was at least 5 months (Seitz JF, etal, ASCO99, Abs. 986:257a).

UFT

In September 1999 the Oncologic Drugs Advisory Committee (ODAC) unanimously recommended UFT (Orzel; Bristol-Myers Squibb) capsules, in combination with leucovorin calcium tablets, for first-line treatment of metastatic colorectal cancer (see FO, pp 811-12, 481 and 55). ODAC concluded that this oral combination regimen, the first ever for advanced colorectal cancer, results in a similar survival outcome as current IV standard therapy for first-line treatment of metastatic colorectal cancer.

ODAC's recommendation was based primarily on results from two randomized multicenter phase III clinical trials, BMS-011 and the BMS-012, that were conducted to evaluate the safety and efficacy of the oral UFT/leucovorin regimen as compared to the standard IV 5-FU/leucovorin regimen in metastatic colorectal cancer. The BMS-011 clinical trial that enrolled 816 patients at 85 centers throughout the USA, Europe and Canada, was the largest registrational phase III clinical trial ever conducted in advanced colorectal cancer. In BMS-011, patients were randomized to UFT (300 mg/m^2) and leucovorin (75 or 90 mg), administered orally, daily, for 28 days, every 35 days, or 5-FU (425 mg/m^2), and leucovorin (20 mg/m^2) administered IV, daily, for 5 days, every 28 days.

Results from these two trials, that enrolled nearly 1,200 colorectal cancer patients, demonstrate that the UFT/leucovorin regimen is equivalent to and significantly safer than the current standard IV chemotherapy. The median survival time for the UFT/leucovorin combination therapy is similar to the current standard therapy of IV 5-FU/leucovorin (12.4 months versus 12.6 months). In the individual studies, UFT plus leucovorin was associated with significantly lower toxicities, such as myelosuppression (including infections), and significantly fewer nonhematologic toxicities, such as stomatitis and mucositis, compared to IV 5-FU/leucovorin. The incidence and/or severity of other side effects observed in the studies, such as diarrhea, nausea and vomiting, were comparable in both regimens. In addition, a reduced need for supportive therapy and concomitant medications, including antiemetics, antibiotics, and growth factors, was observed in patients treated with the oral UFT/leucovorin regimen.

Despite a unanimous recommendation, ODAC agreed that UFT did not represent an advance over standard therapy in metastatic colorectal cancer. Closer scrutiny of the data even revealed a lower overall survival, albeit by only 2.8 months, and a similar QoL between UFT and standard therapy. Therefore, because UFT was not deemed to be a significant therapeutic modality, the FDA may request that

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BMS provide proof that uracil which is combined with tegafur in UFT, does actually contribute to UFT's therapeutic profile. Such a request may delay approval of this agent.

UFT is one of the most commercially successful oncology drugs in Japan with estimated 1997 sales of $430 million (see FO, pp 811-812). In addition to colorectal cancer, UFT has been approved for many other indications in Japan, including breast cancer. The drug, because of its oral bioavailability, and relatively low toxicity, is being prescribed extensively by Japanese physicians. One use, as monotherapy in the adjuvant setting of breast cancer, has been particularly controversial because the gold standard in the USA and Europe is polychemotherapy, as confirmed by clinical trials. Japanese oncologists have also voiced disapproval regarding an ongoing phase III clinical trial in breast cancer (N.SAS-BC) 01, being conducted under the auspices of the National Surgical Adjuvant Breast and Bowel Project (NSABP), in collaboration with the National Cancer Center in Japan. Many believe that the trial is unethical because it is most likely exposing patients to a less effective treatment modality.

The NSABP, based at Allegheny General Hospital (Pittsburgh, PA), also recently closed a landmark adjuvant colon cancer clinical trial (C-06), after enrolling more than 1,600 patients, to evaluate the safety and efficacy of oral UFT/leucovorin as compared to the standard IV 5-FU/leucovorin chemotherapy, in early-stage colon cancer.

Editors note: *Part II of this article will describe the market status of various chemotherapeutics and biologicals, currently in clinical use, and other drugs used as adjunct therapies to mitigate the complications associated with cancer and its treatment.*

MEETING COVERAGE

CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

FROM THE 35TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, ATLANTA, GA; MAY 15-18, 1999

Lung cancer, both early-stage and advanced, represents a new global opportunity for chemotherapeutics. The dominant form of lung cancer, non-small cell lung cancer (nsclc), accounts for about 80% of the cases in the USA, as well as the majority of cases globally. A detailed review of the state-of-the-art in the management of nsclc will be presented in an upcoming issue of FUTURE ONCOLOGY.

APPROACHES TO MAXIMIZE THE ROLE OF CHEMOTHERAPHY IN NSCLC

Many variables enter in the decision making tree regarding treatment choices for nsclc, including disease stage (Stage 0/I=localized, Stage II/III=invasive tumor/nodal spread, and Stage IV=distant metastasis), resectability, patient age and health status, among others.

There are three treatment options in nsclc, namely surgery, radiation therapy (RT) and chemotherapy, used singly or in any combination. Historically, nsclc was almost exclusively treated by surgery, if resectable, and/or RT. However, currently, there is considerable disagreement among oncologists as to the optimal treatment of nsclc. Although surgery remains the gold standard in resectable early disease, and RT in disease that has metastasized to the lymph nodes, numerous chemotherapeutic regimens are being attempted in locoregional/advanced nsclc with varying results.

Investigators at Vanderbilt Cancer Center (Nashville, TN) conducted both a USA and an international survey to establish trends and practice patterns in the treatment of nsclc. In the international survey, among 450 participants from 49 countries, there were 254 (54%) medical oncologists, 86 (18%) radiation oncologists, 79 (17%) pulmonologists, and 16 (1%) others.

In metastatic disease, according to the international survey results, chemoradiotherapy was the most common choice (37%) as adjuvant treatment of T1/2, N1/2 nsclc. Mediastinal RT came second (26%), followed by chemotherapy alone (19%), and no treatment (18%). Differences were observed when the results of this international survey were compared to an earlier survey conducted in the USA (n=980). For instance, for this indication, international radiation oncologists preferred chemoradiotherapy (46%) while those in the USA chose mediastinal RT (56%). However, medical oncologists in both surveys chose chemoradiotherapy first (48% and 39%).

For non-metastatic nsclc, in addition to surgery and/or radiation, international oncologists favored chemotherapy in Stage IIIa/IIIb disease (45%). For unresectable disease, chemotherapy was favored by 32% of respondents. International medical oncologists are more in favor of chemotherapy in earlier-stage lung cancer than USA medical oncologists (17% versus 6%).

In the international survey, the carboplatin/paclitaxel regimen was chosen by 19% of medical oncologists and 11.3% of radiology oncologists, compared to 59% of medical oncologists and 29% of radiation oncologists in the USA survey.

Concurrent chemoradiotherapy (60 Gy) and induction chemotherapy, followed by RT (60 Gy), were considered the best approach for chemoradiotherapy by all groups (35% and 34%, respectively). However, although 73% responded positively when asked whether chemotherapy was appropriate for asymptomatic patients with metastatic nsclc, only 58% of international radiation oncologists versus 72% of medical oncologists, and 60% of USA radiation oncologists versus 83% of medical oncologists, felt chemotherapy was appropriate. Only 18% of oncologists recommend chemotherapy for poor performance patients (Shyr Y, etal, ASCO99, Abs. 1843:478a).

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Exhibit 5
Lung Cancer Incidence and Deaths in the Triad in 1999

Country	Males (#)	Rate*	Females (#)	Rate*	Total (#)	Rate*
			Incidence			
Europe	315,208	83.30	71,327	17.78	386,529	49.59
NA America	106,129	72.69	83,577	54.88	189,706	63.79
Japan	33,374	54.18	12,468	19.44	45,842	36.81
Triad, Total	454,711	77.60	167,372	27.10	622,077	51.69
			Deaths			
Europe	287,952	76.10	62,632	15.62	350,586	44.98
NA America	101,282	69.37	72,642	47.70	173,924	58.54
Japan	27,245	44.23	9,979	15.56	37,224	29.90
Triad, Total	416,479	71.07	145,253	23.52	561,734	46.67

**per 100,000 population*

Source: adapted from Ferlay J, etal, Globocan 1: Cancer Incidence and Mortality Worldwide, IARCPress: Lyon 1998

Postoperative Adjunct Chemotherapy in Resected Disease

Chemotherapy is becoming more common in completely resected locally-invasive nsclc that was historically treated by surgery alone, or surgery plus chemotherapy. However, a large-scale, multicenter, phase III clinical trial [Eastern Cooperative Oncology Group (ECOG) Intergroup Trial E3590], undertaken to determine if concomitant chemoradiotherapy was superior to RT alone in prolonging survival and preventing local tumor recurrence in patients with completely resected Stage II and IIIa nsclc, concluded that adjuvant chemoradiotherapy does not prolong survival in such patients when compared to RT alone.

In this trial, 488 patients, recruited between April 1991 and February 1997, who had undergone complete resection of the primary tumor, and a thorough mediastinal lymph node sampling, or dissection, were randomized to either four cycles of cisplatin (60 mg/m2) delivered on day 1, and etoposide (120 mg/m2), on days 1-3, administered concurrently with RT (5040 cGy) in 28 daily 180 cGy fractions, or RT alone, at this same dose. Among 351 patients eligible for analysis at a median follow-up of 37 months, 183 were treated with chemoradiotherapy and 168 with RT alone. In the chemoradiotherapy arm, 66% (121/183) of patients were treated with all four cycles of chemotherapy, while 76% (139/183) were treated with RT. In the RT arm only, 83% (139/168) of patients were treated with the requisite RT dose.

Grade 3/4 toxicity, consisting largely of leukopenia and esophagitis, occurred in 8.8% and 1.3% of patients treated with RT alone, and 25% and 65% with chemoradiotherapy, respectively. Treatment-associated mortality was 2.2% in the chemoradiotherapy arm, and 2.4% in the RT arm. At 40.5 months follow-up, median survival of all patients randomized to RT only was 38.2 months, and 37.6 months for those randomized to combination therapy. Five-year survival was projected at 39% in the RT arm, and 33% in the combined arm. Similarly, analysis of stratified subgroups showed no statistically significant survival advantage for either treatment arm. Median survival of all patients with N1 disease was 45.2 months, and of those with N2 disease, was 30.6 months. Despite its negative findings, this trial demonstrated the feasibility of designing and completing a prospective multimodality lung cancer trial in the cooperative group setting, rather than relying on historic controls (Keller SM, etal, 1999; ASCO99, Abs. 1793:465a).

Neoadjuvant Chemotherapy in Resectable Disease

Several randomized clinical trials conducted in the early 1990s indicated that there was a survival advantage in neoadjuvant chemotherapy over surgery alone in resectable Stage IIIa nsclc (Roth IA, etal, JNCI 1994; 86:673-680, and Rosen R, etal, NEJM 1994;330:153-158). Currently, although neoadjuvant chemotherapy represents standard treatment in some institutions for resectable Stage IIIa nsclc, and may be applicable in earlier disease, its true impact on survival has not been categorically established. Also, current data reveals that certain preoperative chemotherapies increase perioperative complications and mortality. Therefore, there is a need for strategies to prevent such complications if more patients were to be treated by chemotherapy prior to resection.

The impact of neoadjuvant chemotherapy was assessed in one study, conducted at Vanderbilt University, in which the outcome of 25 patients who underwent lobectomy or pneumonectomy after neoadjuvant carboplatin and paclitaxel therapy (2-3 cycles), was compared to 55 patients resected without preoperative therapy. Neither group was treated with preoperative RT. Complications were analyzed as life-threatening (pneumonia, intubation, or transfer to ICU), major (prolonging hospital stay but not dangerous), and minor.

Striking increases were found in the incidence of life-threatening complications, and reintubation and tracheostomy, in patients treated with neoadjuvant chemotherapy. The incidence of life-threatening complications was 7.3% in those treated by surgery alone, compared to 32% in the neoadjuvant chemotherapy group. Among those who did most poorly, i. e. chemotherapy patients with large resections, there were 8 life-threatening complications, 7 being pneumonias, none apparently attributable to aspiration. Interestingly, 3 of the pneumonias were

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Exhibit 6
Global Sales of Selected Anticancer Drugs and Related Products

Company	Generic Name ❑ Brand Name	1998 WW ($mil.)	Change (%)
	Anticancer Drugs		
Alza (Sequus Pharmaceuticals) ❑ Schering- Plough	Doxorubicin HCl ❑ Doxil (USA); Caelyx (outside the USA)	42.5[1]	55.6
AstraZeneca	Anastrozole ❑ Arimidex	121.0	42.3
AstraZeneca	Goserelin ❑ Zoladex	629.6	8.4
AstraZeneca	Tamoxifen ❑ Nolvadex	527.7	3.8
AstraZeneca	Bicalutamide ❑ Casodex	245.5	20.5
AstraZeneca	Raltitrexed ❑ Tomudex	21.7[2]	
Aventis (Hoechst Marion Roussel)	Nilutamide ❑ Nilandron	45.5	299.8
Aventis (Rhône-Poulenc Rorer)	Irinotecan ❑ Campto	52.3[2]	
Aventis (Rhône-Poulenc Rorer)	Docetaxel ❑ Taxotere	374.0	
Barr Laboratories	Tamoxifen	—[1,3]	
Berlex Laboratories (Schering AG)	Fludarabine phosphate ❑ Fludara	80.1	
Bristol-Myers Squibb	Paclitaxel ❑ Taxol	1,206.0	
Bristol-Myers Squibb	Carboplatin ❑ Paraplatin	525.0	20.1
Bristol-Myers Squibb	Cisplatin ❑ Platinol	132.0	(9.0)
Bristol-Myers Squibb	Etoposide ❑ VePesid	84.0	12.5
Centocor ❑ Glaxo Wellcome	Edrecolomab ❑ Panorex	3.0[2]	(50.0)
Chiron	Aldesleukin ❑ Proleukin	93.0	32.9
Eli Lilly	Raloxifene ❑ Evista	133.0[4]	
Eli Lilly	Gemcitabine ❑ Gemzar	306.8	75.5
Genentech	Trastuzumab ❑ Herceptin	30.5[1]	N/A
Glaxo Wellcome	Vinorelbine ❑ Navelbine	63.0	3.8
Guilford Pharmaceuticals	Prolifeprosan 20/carmustine ❑ Gliadel	6.5	
Hoffmann-La Roche	Doxifluridine ❑ Furtulon	149.5[2]	1.2
Hoffmann-La Roche	Interferon αlfa-2a ❑ Roferon-A	227.2[5]	2.0
IDEC Pharmaceuticals ❑ Genentech, Hoffmann-La Roche	Rituximab ❑ Rituxan (USA), MabThera (Europe)	162.6	
Immunex	Mitoxantrone ❑ Novantrone	48.8	(5.0)
Immunex	Thiotepa ❑ Thioplex	24.9	11.0
Johnson & Johnson	Cladribine ❑ Leustatin	53.0	
NeXstar Pharmaceuticals	Daunorubicin ❑ DaunoXome	4.7	
Norvartis	Pamidronate ❑ Aredia	391.0	58.4
Novartis	Fadrozole ❑ Afema	55.2[2]	3.9
Norvartis	Letrozole ❑ Femara	100.5	175.0
Norvartis	Formestane ❑ Lentaron	38.0[2]	10.0
Nycomed Amersham	Rapidstrands (brachytherapy seeds)	69.7	
Orion Pharma ❑ Schering-Plough	Toremifene ❑ Fareston	17.0	
Pharmacia & Upjohn	Irinotecan, CPT-11 ❑ Camptosar	194.0	26.0
Pharmacia & Upjohn	Epirubicin ❑ Ellence (USA) Farmorubicin, Pharmorubicin	177.3[2]	(9.3)
QLT Phototherapeutics	Porfimer sodium ❑ Photofrin	8.8	
Sanofi-Synthelabo ❑ Eli Lilly	Oxaliplatin ❑ Eloxatin	40.0[2]	110.5
Schering AG	Cyproterone acetate ❑ Cyprostat, Androcur	197.0	

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Schering-Plough	Flutamide ❑ Eulexin	171.0	(20.1)
Schering-Plough ❑ Orion Pharma	Toremifene ❑ Fareston	52.0[6]	
Schering-Plough	Interferon α-2b ❑ Intron A/Rebetron	719.0[7]	N/A
SmithKline Beecham	Topotecan ❑ Hycamtin	118.6	38.0
Takeda	Leuprolide acetate ❑ Leuplin	271.0[2]	13.3
TAP Holdings	Leuprolide acetate ❑ Lupron, Lupron Depot, Enantone (Germany)	1,025.0[8]	(13.3)
	Treatment Adjuncts		
American Home Products	Oprelvekin ❑ Neumega	49.0	
Amgen	Epoetin-α ❑ Epogen	1,380.0[2, 9]	19.0
Amgen-Kirin ❑ Sankyo	Epoetin-α ❑ Espo	434.0[2, 9]	
Amgen	Filgrastim ❑ Neupogen	1,120.0	5.7
Amgen ❑ Sankyo	Filgrastim ❑ Gran	107.0[2]	(8.4)
Aventis (Rhône-Poulenc Rorer)	Lenograstim ❑ Granocyte	81.5	14.3
Boehringer Mannheim (Hoffmann-La Roche)	Epoietin-β ❑ Recormon	650.0	
Chugai Pharmaceutical	Lenograstim ❑ Neutrogin (Japan)	165.0[2]	
Chugai Pharmaceutical	Epoietin-β ❑ Epogin	416.6[2, 9]	5.9
Glaxo Wellcome	Ondansetron ❑ Zofran; Zofran ODT	649.5	4.8
Hoffmann-La Roche	Filgrastim ❑ Neupogen	241.3[2]	(29.0)
Hoffmann-La Roche	Ibandronate ❑ Bodronat	55.2[2]	
Immunex	Sargramostim ❑ Leukine, Interberin, Prokine	63.8	21.0
Johnson & Johnson (Ortho Biotech and Janssen-Cilag)	Epoetin α ❑ Procrit, Eprex (outside the USA), Erypo (Germany)	1,271.0	16.6
The Liposome Company	Amphotericin B lipid complex ❑ Abelcet	73.5	26.0
MGI Pharma	Pilocarpine HCl ❑ Salagen	12.3	
NeXstar Pharmaceuticals	Amphotericin B ❑ AmBisome	109.9	
Novartis	RhGM-CSF ❑ Leucomax	52.4	5.6
Novartis	Ocreotide ❑ Sandostatin	311.0[10]	34.0
SmithKline Beecham	Granisetron ❑ Kytril	351.4	6.5
Unimed Pharmaceuticals	Dronabinol ❑ Marinol	10.3	27.0
U.S. Bioscience ❑ Alza, Schering-Plough	Amifostine ❑ Ethyol, Ethiofos, Gammaphos	32.6	

[1] USA only
[2] Outside the USA
[3] Sells tamoxifen purchased from AstraZeneca
[4] Sales for prevention/treatment of osteoporosis only
[5] Sales for oncology and hepatitis indications
[6] Now being marketed by Roberts Pharmaceuticals
[7] Sales include those of Rebetron, a combination of Intron A and Rebetrol, for the treatment of hepatitis C.
[8] Includes sales for treatment of endometriosis
[9] Sales for renal dialysis-related anemia only
[10] Main indication is acromegaly
Source: NEW MEDICINE Oncology KnowledgeBASE (nm|OK), July 1999.

pseudomonal. In addition, the incidence of intubation was 20% in those who underwent neoadjuvant chemotherapy compared to 3.7% in those who underwent surgery alone, and the incidence of tracheostomy was 12% versus 0%, respectively. There was no hospital mortality in either group but 2 patients who were treated with neoadjuvant chemotherapy, died after discharge from the hospital, from pneumonia and pulmonary embolus, respectively.

This difference was significant and, generally, neoadjuvant chemotherapy increased the perioperative complications in this cohort of patients compared to a similar cohort resected by the same surgeon (Roberts JR, etal, ASCO99, Abs. 1794:465a).

However, another study using a non-paclitaxel neoadjuvant regimen showed a survival benefit among those in the neoadjuvant chemotherapy group, despite a high inci-

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dence of perioperative complications. This phase III 38-center clinical trial of neoadjuvant chemotherapy, conducted by the French Thoracic Cooperative Group, (Besançon, France), enrolled, between July 1991 and April 1997, 373 patients with resectable Stage I (except T1N0), II and IIIa nsclc. Patients were randomized to either surgery alone (arm 1=186 patients), or surgery with neoadjuvant MIP chemotherapy (arm 2=187 patients) which consisted of two cycles of mitomycin (6 mg/m^2), ifosfamide (1.5 g/m^2), and cisplatin (30 mg/m^2), administered at a 3-week interval; 2 more cycles were administered postoperatively to those with objective responses. In both arms, patients with Stage IIIa disease were administered postoperative thoracic RT. Among the 355 evaluable patients (Stage I/II=188 and Stage IIIa=167), surgery was performed in 174 patients in arm 1 and 169 in arm 2.

There were 19 CR (11%) and 95 PR (53%). RT was delivered to 72 patients in arm 1, and 41 in arm 2. As of September 1, 1998, median survival was 26 months in arm 1, and 36 in arm 2, with 1-, 2- and 3-year survival rates at 73%, 52% and 41% in arm 1, and 77%, 59% and 49% in arm 2, respectively. After a non-significant excess of deaths in arm 2 during the treatment period, especially by bronchopleural fistula (n=6), the effect of neoadjuvant chemotherapy after 150 days significantly favored survival. Benefit from neoadjuvant chemotherapy was confined to N0-1 patients with disease-free survival being significantly longer in the neoadjuvant chemotherapy arm in this group. However, although neoadjuvant chemotherapy offers a survival advantage in resectable nsclc, there is high perioperative toxicity (Depierre A, etal, ASCO99, Abs. 1792: 465a). An important contributor to the high early toxicity associated with the MIP regimen is probably mitomycin C that leads to frequent postoperative pulmonary complications with a mortality rate ranging between 5% to 15%.

In a phase II clinical trial without a comparator arm, conducted by the Swiss Group for Clinical Cancer Research (SAKK), a novel regimen of neoadjuvant chemotherapy involving the combination of docetaxel and cisplatin, produced favorable results in the treatment of Stage IIIA-N2 nsclc. Docetaxel (85 mg/m^2) on day 1 and cisplatin (40 mg/m^2) on days 1 and 2, were administered preoperatively, for 3 times, at 3-week intervals in 34 patients. Those with PR, CR, or stable disease, underwent radical resection including mediastinal lymphadenectomy. Postoperative RT was administered if the resection was not complete and/or the first mediastinal lymph node was involved. Grade 3 toxicity involving diarrhea, paresthesia, pneumonia, and fatigue, occurred in 4 cycles/patients. There was one fatality from gastric bleeding. Grade 3/4 hematologic toxicity involved granulocytopenia.

The overall response rate (RR) among 32 evaluable patients was 21/32 (66%), with 4/32 (12%) CR and 17/32 PR (53%); disease stabilized in 30%, and progressed in 6%. Downstaging with negative first mediastinal lymph node at surgery occurred in 60% of patients, and complete resection was possible in 70%. There were no postoperative pulmonary complications but one patient died from a heart attack on day 4 after surgery (Betticher DC, etal, ASCO99, Abs. 1824:473a).

Similarly, in a phase II clinical trial (EORTC 08958), a paclitaxel and carboplatin induction chemotherapy regimen was well tolerated and active in the neoadjuvant setting involving 57 chemotherapy- and RT-naive patients with pathologically confirmed, mediastinoscopy proven, Stage IIIa/N2 nsclc. Patients were treated with up to 3 courses of neoadjuvant paclitaxel (200 mg/m^2) as a 3-hour infusion with premedication, followed by carboplatin (AUC 6), from March 1997 to September 1998. Patients were also registered for the ongoing EORTC 08941 trial comparing surgical resection with radical RT after chemotherapy. Among 40 evaluable patients for response, and 43 for toxicity, the objective RR was 59%. There were no CR, and disease stabilized in 18% of patients and progressed in the rest. Grade 3/4 toxicity was exclusively hematologic including leucopenia (2%), neutropenia (52%), and anemia (2%); there was one case of neutropenic fever (2%). Grade 3 toxicity included lethargy (9%), sensory neuropathy (5%), with one documented case (2%) of motor neuropathy, anorexia, nausea, vomiting, skin toxicity, dyspnea, arthralgia and myalgia. Grade 2 alopecia occurred in 52% and Grade 3 in 35% of patients (O'Brien MER, etal, ASCO99, Abs. 1898:492a).

In a phase II clinical trial, conducted by the Minnie Pearl Cancer Research Network to compare adjuvant and neoadjuvant chemotherapy, a paclitaxel and carboplatin regimen was used in 71 patients with early-stage (Stage Ib or II) nsclc. Overall, 49 patients [Stage Ib=18, Stage II=31 (IIa=7; IIb=24)] were fully evaluable. The 26 patients (Stage Ib=10; II=16) in the neoadjuvant group were treated with paclitaxel (200 mg/m^2) and carboplatin (AUC=6), every 3 weeks, for 3 cycles, and the 23 patients (Ib=8; II=15) in the adjuvant group were treated with paclitaxel and carboplatin for 3 cycles. Patients with Stage II nsclc in the neoadjuvant group, were also treated with thoracic RT and postoperative weekly paclitaxel (50 mg/m^2) and carboplatin (AUC=2) for 6 weeks. Those with Stage II disease in the adjuvant group were also treated with RT and weekly chemotherapy after the initial 3 cycles of chemotherapy.

All 3 cycles of either neoadjuvant (24/26) or adjuvant (22/23) chemotherapy were completed by 46/49 patients. Of the 23 patients in the adjuvant chemotherapy group, 17 remained progression free, and 6 relapsed, at a median follow-up of 14 months. Of the 26 patients in the neoadjuvant chemotherapy group, 9 (Ib=4, IIa=1, IIb=4) were medically inoperable at diagnosis. These patients were treated first with adjuvant chemotherapy, and then with thoracic RT (60 Gy), concurrently with weekly paclitaxel (50 mg/m^2) and carboplatin (AUC=2), for 6 weeks. Although 17 of the 26 patients in the neoadjuvant chemotherapy group were candidates for resection at the time of diagnosis, 5 did not have surgery. Among the 12 patients whose tumors were

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Exhibit 7
Select Platinum-based Drugs in Development

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status➢ Location ❑ Indication(s)
Access Pharmaceuticals ❑ U London School of Pharmacy	Polymer platinate ❑ AP5070	Soluble, synthetic polymer conjugate formulation of cisplatins ❑ injection	Preclin (o5/99)➢UKs ❑ first-line treatment of solid tumors
Alza (Sequus Pharmaceuticals) ❑ Sicor	SPI-77 or SPI-077	STEALTH liposome cisplatin; liposomal formulation of cisplatin in long-acting Stealth liposomes ❑ IV	Phase II (o5/98)➢USA ❑ solid tumors; phase II (b3/98)➢USA ❑ nsclc
Aronex Pharmaceuticals ❑ U Texas M.D. Anderson Cancer Center	AR726 ❑ Platar	Novel platinum analog; liposomal formulation ❑ IV, intraperitoneal	Phase II (o9/99)➢USA ❑ mesothelioma, metastatic renal cell carcinoma
AstraZeneca ❑ AnorMED, Cancer Research Campaign	ZD0473	A novel sterically hindered platinum complex designed primarily to be less susceptible to inactivation by thiols; 3rd generation compound with activity against cisplatin- or carboplatin-resistant tumors ❑ IV	Phase I (o5/99)➢UK ❑ advanced solid tumors
Boehringer Mannheim (Hoffmann-La Roche)	BBR 3464	Trinuclear platinun complex	Phase I (b6/98)➢USA ❑ solid tumors
Bristol-Myers Squibb (BMS) ❑ Johnson Matthey	JM216, BMS-182751	Novel oral platinum (IV) analog ❑ PO	Phase II (c97)➢USA; phase III (o6/98)➢Europe ❑ nsclc; phase I (o5/99)➢USA ❑ advanced, refractory solid tumors, head and neck cancer; phase II (c98)➢USA, phase III (o98)➢Europe ❑ hormone-refractory prostate cancer; phase II (98)➢USA ❑ advanced, incurable, or recurrent cervical cancer
Matrix Pharmaceutical	Cisplatin/epinephrine ❑ IntraDose-CDDP Injectable Gel	Biodegradable injectable collagen-based gel-like matrix of cisplatin/epinephrine ❑ intratumoral	Phase III (o8/99)➢USA, Europe ❑ advanced head and neck cancer; phase III (c1/99)➢USA, Europe ❑ accessible solid tumors; phase II (o8/99)➢USA, Europe ❑ liver cancer, metastatic colorectal cancer; phase II (o8/99)➢USA, Europe, Hong Kong ❑ primary, inoperable hepatocellular carcinoma
Shionogi	Nedaplatin	Second generation platinum complex with reduced nephrotoxicity ❑ IV	Research (o4/99)➢Japan ❑ lung cancer
SuperGen ❑ Janssen Biotech, Cyclex	Cisplatin ❑ Cisplatin Extra	Reformulation of cisplatin to increase solubility and decrease hypersensitivity and other reactions seen with the current formulation ❑ injection	Phase III (o1/99)➢USA ❑ solid tumors
Syren Pharmaceuticals ❑ ISIS Innovation	Terpyridine-platinums	A platinum-based compound which can overcome resistance to existing platinum-based chemotherapy in tumor cells;inhibits proliferation of tumor cells	Research (o10/98)➢UK ❑ solid tumors
U Texas M.D. Anderson Cancer Center	DACH-acetato-Pt (1R, 2R-diaminocyclohexane) (trans-diacetato)(dichloro)-platinum ❑ IV	Novel platinum (IV), a cisplatin analog with superior antitumor activity than cisplatin; more efficiently induces p53 protein and activates p53 functions ❑ injection	Preclin (o99)➢USA ❑ cisplatin-resistant ovarian tumors expressing wild-type p53

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Unitech	Neoplatin	Novel patented formula of cisplatin ❑ IV	Preclin (o8/99)➢USA ❑ breast and skin cancer
Unitech		Novel compositions of cisplatin, a special carrier and, optionally, customary pharmaceutical excipients; composition comprising cisplatin and folic acid ❑ IV	Preclin (o8/99)➢USA ❑ solid tumors
Unitech		Novel cisplatin analogs with a larger molecular size; may have more stereoselectivity compared to cisplatin ❑ IV	Research (o8/99)➢USA ❑ solid tumors
Unitech		Cisplatin analogs; dinuclear platinum complexes involving two platinum ions in one molecule (inter and intro linkage) ❑ IV	Research (o8/99)➢USA ❑ solid tumors
Unitech		Analogs of carboplatin	Research (o8/99)➢USA ❑ solid tumors

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

resected, there were 2 CR (16.7%), 9 PR (75%) and disease stabilized in 1 (.08%); 10 remained progression free at 8+ months and 26+ months, and 2 progressed/died at 4 months and 11 months. Tumors progressed in 11/31 patients with Stage II nsclc, and 5/18 patients with Stage Ib nsclc (neoadjuvant=10, and adjuvant=6).

The 3 cycles of this regimen were relatively well tolerated and there were no treatment-related deaths. The combined RT and weekly chemotherapy was administered to 90% of eligible patients (60% as scheduled). Grade 3/4 esophagitis was the most common toxicity (25%). Severe lung toxicity occurred in only one patient. Use of this combined modality regimen in either the neoadjuvant or adjuvant settings for early stage nsclc is feasible and relatively safe (Greco, FA, etal, ASCO99, Abs. 1952:506a).

A study was conducted at the Catholic University (Leuven, Belgium) to assess the correlation between downstaging, survival, and pretreatment staging. Between March 1995 and August 1998, 46 consecutive patients with pathology-proven N2 disease were treated with three cycles of a three-drug (vindesine, ifosfamide and cisplatin) combination regimen, and underwent a rigorously performed cervical mediastinoscopy. Patients with at least a PR (n=26) were surgically explored. RR to chemotherapy was 57% (26/46), resection was completed in 23/26 (88.5%) of responders with pneumonectomy performed in 16/23; in 11 patients (42.9%) the mediastinal nodes which were positive at mediastinoscopy, were negative (downstaging group) after chemotherapy. The projected 2-year survival of resected patients is 41%. Patients with node downstaging did not survive longer compared to those without downstaging. Surgery in N2-patients responsive to induction chemotherapy resulted in a high complete resectability rate. Findings at pre-treatment mediastinoscopy proved to be the most important prognostic factor (De Leyn P, etal, Eur J Cardiothorac Surg, May 1999;15(5):608-14).

Neoadjuvant Chemoradiotherapy in Resectable Disease

Neoadjuvant chemoradiotherapy conferred a significant survival advantage in locally-advanced nsclc according to a randomized clinical trial performed in the late 1980s (Dillman RO, etal, NEJM 1990;323:940-945). However, adding radiation to chemotherapy in the neoadjuvant setting may significantly increase the complication rate. Interim results from an ongoing randomized clinical trial, to enroll 350 patients with Stage III nsclc, indicate that the addition of RT increased the perioperative mortality rate, and the incidence of Grade 3/4 toxicity (Thomas M, etal, ASCO99, Abs. 1769:458a).

However, at the University of Pennsylvania (Philadelphia, PA), patients with Stage IIIa nsclc who strongly desire surgery, are offered preoperative chemoradiotherapy which is well tolerated, with high rates of resectability and pathologic responses. In January 1997, this institution changed the chemotherapy regimen from a cisplatin/etoposide combination to that of carboplatin/paclitaxel mostly because it is suggested that chemoradiotherapy using a carboplatin/paclitaxel combination may be better tolerated.

In a small nonrandomized study, conducted between January 1995 and July 1998, the toxicity and efficacy of these two trimodality regimens were compared in 31 patients with mediastinoscopy-proven Stage IIIa nsclc. Patients were treated with RT (45-54 Gy) and either cisplatin/etoposide (Group A) during weeks 1 and 5, or carboplatin/paclitaxel (Group B), usually administered weekly. The two groups were similar with respect to pretreatment characteristics. 'Major' toxicity was defined as that requiring hospitalization and 'major' pathologic response was defined as downstaging to Stage I, with 'minimal' residual foci of carcinoma in the primary tumor. All patients

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successfully completed induction chemoradiotherapy, which was well tolerated, with an overall resectability rate of 80%. The median postoperative hospital stay was 7 days. There were 14 major PRs (56% of resectable patients and 45% of all patients) and 3 pathologic CRs (two in Group A, one in Group B). Two patients died from postoperative complications (one in each group). Median survival had not been reached at the time of this presentation; 1-year actuarial survival was 74% (Algazy KM, etal, ASCO99, Abs. 1906:494a).

Induction Chemotherapy and Concomitant Chemoradiotherapy in Unresectable Stage III Disease

Cisplatin, in combination with vinorelbine, or gemcitabine, or paclitaxel, can be safely administered as induction chemotherapy and concomitant chemoradiotherapy in patients with unresectable Stage III nsclc. In a randomized, phase II clinical trial (CALGB 9431), 181 therapy-naive patients with unresectable Stage III nsclc were treated with two cycles of induction chemotherapy using three separate regimens combining an induction regimen consisting of cisplatin with vinorelbine, or gemcitabine, or paclitaxel, and concomitant chemoradiotherapy. Patients were treated with 4 cycles of cisplatin (80 mg/m^2), on days 1, 22, 46, 64, and gemcitabine (1250 mg/m^2), on days 1, 8, 22, 29; or paclitaxel (225 mg/m^2 over 3 hours on days 1, 22, and 135 mg/m^2 on days 43 and 64); or vinorelbine (25 mg/m^2 on days 1, 8, 15, 22, 29 and 15 mg/m^2 on days 43, 50, 64, 71). RT began on day 43 at 200 cGy, daily, for a total dose of 66 Gy.

Treatment-induced toxicities in the vinorelbine, paclitaxel and gemcitabine treatment arms, prior to RT, were primarily Grade 3/4 granulocytopenia (52%, 52%, 46%, respectively), and with RT were Grade 3/4 thrombocytopenia (0%, 6%, 53%, respectively), and esophagitis (25%, 31%, 49%, respectively). Overall best response was as follows:

Response Type	Gemcitabine (%)	Paclitaxel (%)	Vinorelbine (%)
Induction Chemotherapy			
CR	0	0	2
PR	27	27	34
Regression	3	0	0
Total	30	27	36
Induction Chemotherapy and Chemoradiotherapy			
CR	2	12	10
PR	56	38	45
Regression	3	0	2
Total	61	50	57

The best response to induction chemotherapy was 36% in the vinorelbine group, 27% in the paclitaxel group, and 30% in the gemcitabine group. Overall best response was 57% in the vinorelbine group, 50% in the paclitaxel group, and 61% in the gemcitabine group. At a median follow-up of 9 months, median survival for all patients was 18 months, one-year survival was 66%, and median failure-free survival was 10 months (Vokes EE, etal, ASCO99, Abs. 1771:459a).

Because both accelerated RT as well as induction and concomitant cisplatin-based chemotherapy demonstrated survival advantages in randomized trials in locally advanced nsclc, a phase II clinical trial was undertaken to assess the impact of docetaxel and cisplatin induction and concomitant chemotherapy, combined with accelerated RT, in Stage III nonresectable nsclc (Nyman J and Mercke C, ASCO99, Abs. 1998:518a). Between December 1996 and October 1998, 20 consecutive patients with locally advanced nsclc (Stage IIIa=4 and Stage IIIb=16) were treated at Gothenburg University in Sweden with 3 courses of docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) on day 1; the third course was administered with concomitant RT (64.6 Gy) in two daily fractions of 1.7 Gy. There was an interval of one week after 40.8 Gy was administered, resulting in 4.5 weeks of treatment, and a total of 57 cycles. Grade 3/4 neutropenia was seen in 45%, febrile neutropenia in 12%, and thrombocytopenia in 2%. Nonhematologic toxicity included Grade 2/3 asthenia in 51%, fluid retention in 2%, and diarrhea in 12%. One patient (6%) suffered Grade 3 esophagitis and 12 (67%) Grade II. There were 2 patients with Grade 2 pneumonitis, and one patient died of pneumonitis 3 months after completion of therapy. A very high RR was achieved with this combined therapy with manageable toxicity. After 2 cycles of chemotherapy there were 13 PR (65%) and disease stabilized in 6. Among 16 evaluable patients, 3 months after RT, there were 13 PR (81%). Median survival had not been reached at the longest follow-up of 21 months but 8 patients died, 5 of lung cancer.

An NCI-sponsored phase II clinical trial (protocol IDs: RTOG-9807, RTOG-DEV-1001) of paclitaxel and carboplatin, before, and concurrently, with RT in inoperable Stage II or Stage III nsclc, will accrue 57 patients over 10 months to determine the survival rate of patients with inoperable nsclc treated with this regimen, as well as its toxicity, and the thoracic failure rate outside of the irradiated field in these patients. The protocol involves paclitaxel infused over 3 hours followed by carboplatin infused over 30 minutes on days 1 and 22, then filgrastim (G-CSF) injections once daily, on days 4-15, and 25-36. RT is administered twice daily, 5 days per week, over 4 weeks, on days 43-70, and concurrent paclitaxel and carboplatin, is administered on days 43, 50, 57, and 64. Patients are followed every 3 months for 2 years, then every 6 months for 3 years, then annually thereafter.

An NCI-sponsored, phase III randomized clinical trial (protocol ID: CLB-39801), initiated in June 1998 by the Cancer and Leukemia Group B, is comparing concurrent carboplatin, paclitaxel, and RT, with or without prior induction carboplatin and paclitaxel, in unresectable Stage

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III nsclc. The trial, to accrue 360 chemotherapy- or RT-naive patients within 3 years, has been designed to compare the overall RR, disease-free survival, overall survival, toxicity, and effects on locoregional versus distant failure of these two regimens.

Patients are randomized either to:

- arm I for immediate concurrent chemoradiotherapy involving IV paclitaxel administered over 1 hour, followed by IV carboplatin over 30 minutes on day 1, and RT to the chest 5 times-a-week beginning on day 1; treatment is repeated weekly for a total of 7 courses
- arm II for induction chemotherapy, followed by delayed concurrent chemoradiotherapy, involving IV paclitaxel administered over 3 hours, followed by IV carboplatin over 30 minutes; treatment repeats every 3 weeks for 2 courses, and patients then undergo 7 courses of concurrent chemoradiotherapy as in Arm I for a total treatment time of 13 weeks

Patients are followed every 2 months for 2 years, then every 4 months for the next 2 years, and annually thereafter.

Concurrent Versus Sequential Chemoradiotherapy in Unresectable Disease

Although chemoradiotherapy has been shown to be superior to radiation alone in invasive (Stage III) nsclc, the best timing of RT has not been established. A phase III randomized clinical trial was conducted between August 1992 and December 1994, to assess the value of concurrent versus sequential thoracic RT in combination with a regimen (MVP) consisting of mitomycin (8 mg/m^2) and cisplatin (80 mg/m^2) on days 1 and 29 and vepesid (3 mg/m^2) on days 1, 8, 29 and 36, in selected patients with unresectable Stage III nsclc, including those with supraclavicular lymph node metastasis but excluding those with T3N0M0 disease and pleural effusions. In one regimen, thoracic RT (2 Gy fraction for 14 times or 28 Gy) was administered beginning on day two of MVP, for three weeks, and after a rest period of 10 days, 28 Gy were administered for another three weeks. In the other, thoracic RT (56 Gy), administered as a conventional schedule, was started after completion of MVP. Patients responding to chemotherapy in the sequential arm, were administered one or two cycles of chemotherapy after completion of RT. A total of 314/320 patients were evaluable for response, survival, and Grade 3/4 toxicity.

Preliminary results had indicated a survival advantage for the concurrent group. There was one toxic death from sepsis in the concurrent radiation and MVP group, and two patients died from radiation pneumonitis in the sequential radiation group. Other toxicities included neutropenia, 94.2% and 73.4%, respectively, and anemia, 48.7% and 31.8%, respectively (Furuse K, ASCO97, Abs. 1649:459a).

At a five-year median follow-up, survival favored concurrent therapy over sequential therapy, 64.1% versus 54.8% at one year, 34.6% versus 27.4% at two years, 22.3% versus 14.7% at three years, 16.9% versus 10.1% at four years, and 15.8% versus 8.9% at five years. In addition, median survival of 16.5 months and 13.3 months, respectively, also favored concurrent therapy over sequential therapy. Beyond four years, at the time of this presentation, there were 11 survivors in the concurrent therapy group and 7 in the sequential therapy group. In this nsclc population, thoracic RT, concurrent with MVP, resulted in a significant advantage in survival compared with sequential therapy (Furuse K etal, ASCO99, Abs. 1770:458a).

Various different drugs/combinations are currently used in concurrent chemoradiotherapy. One such regimen involving concurrent radiation with paclitaxel and carboplatin, leads to significant esophagitis and pneumonitis. Therefore, a trial was conducted to see if amifostine, added to this regimen would act as a chemo- and radioprotectant. Between October 1996 and November 1998, 20 patients with unresectable nsclc (Stage II=1, Stage IIIa=7, and Stage IIIb=12) were entered in a phase II clinical trial and treated with paclitaxel (170 mg/m^2), administered over 3 hours, and carboplatin (AUC=5), every 4 weeks, for 3 cycles, combined with conformal radiation (6100 cGy). Amifostine was administered at a dose of 740 mg/m^2 with chemotherapy, and at 200 mg/m^2, with RT for 4/5 days. No G-CSF or GM-CSF was used during treatment. Grade 3 toxicities in 43 cycles of chemotherapy (35 with amifostine) included neutropenia (n=10), nausea/vomiting (n=3), thrombocytopenia (n=2), esophagitis (n=2) and pneumonitis (n=1). Amifostine was discontinued in 4 patients among 9 who experienced hypersensitivity reactions; 2 patients also reacted to paclitaxel. Use of feeding tubes or parenteral nutrition was not required in any patients. Among 15 evaluable patients there were 3 (20%) CR and 10 experienced a lesser response than CR. Disease progressed in the brain during therapy in 2 patients. Ten patients have since died (one free of disease). Median survival was 15 months, with the longest survivor alive at 25 months at the time of this presentation (Roychowdhury DF, etal, ASCO99, Abs. 2011:522a).

Postoperative Chemotherapy with or without Radiotherapy in Resected Disease

An NCI-sponsored, phase III randomized multicenter clinical trial (protocol IDs: CLB-9734, NCCTG-C9734) of postoperative paclitaxel and carboplatin with or without adjuvant RT for resected Stage IIIa nsclc, was initiated in May 1998 by the Cancer and Leukemia Group B. Over a 2-year period, the trial will enroll 480 chemotherapy- or RT-naive patients with Stage IIIa nsclc who underwent complete resection with no known residual disease. The trial's objectives are to:

- compare the overall survival of surgically resected patients with limited Stage IIIa nsclc who are treated by postoperative chemotherapy with or without adjuvant RT
- compare failure-free survival

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- describe patterns of local and distant recurrence
- determine the toxicity profile of chemotherapy alone, and of the adjuvant RT in these patients

Four to eight weeks after surgery, 4 courses of chemotherapy are delivered consisting of paclitaxel, administered by a 3 hour continuous infusion, followed by carboplatin, administered over 1-2 hours, on days 1, 22, 43, and 64. Subsequently, patients are randomized into arm I for no further therapy, or arm II involving RT to the mediastinum, 5 days-a-week for 5 weeks, beginning 2.5 to 4 weeks after completion of chemotherapy. Patients are followed at least every 4 months for 2 years, and every 6 months thereafter.

COMMERCIALLY AVAILABLE CHEMOTHERAPEUTICS IN CLINICAL TRIALS IN ADVANCED DISEASE

Numerous combination chemotherapies for various stages of nsclc are under clinical evaluation. Among them, platinum-based combination therapies are the cornerstone of current standard treatment for advanced nsclc. Clinical trials that have also paired paclitaxel with cisplatin, or carboplatin, in both advanced and early-stage nsclc, have produced superior results than the standard etoposide or vinorelbine and cisplatin combination.

According to the Vanderbilt survey (Shyr Y, etal, *ibid*), the most widely favored chemotherapy choice for first-line therapy in Stage IV disease (42%), was the platinum and etoposide regimen, followed by platinum and vinorelbine (14%). International medical oncologists favored the platinum and etoposide regimen (31%), compared to only 14% of USA medical oncologists, but this regimen was the first choice of both international and USA radiation oncologists (46% and 48%, respectively). By region, the platinum and etoposide regimen is widely favored in East Asia (50%), followed by Central/West Asia and Africa (43%), Europe (35%), and the Americas (27%).

Two-drug Combination/Multimodality Therapies

Combination chemotherapy as an adjunct to other modalities, such as resection, if possible, and/or RT, is the standard treatment approach for invasive/metastatic nsclc.

Platinum-based chemotherapy regimens are the mainstay of two-drug combination therapies in nsclc. Various two-drug combinations have been evaluated and several regimens have demonstrated superior RRs and lower toxicity when compared to the traditional cisplatin/etoposide combination. Currently, the combination of paclitaxel and carboplatin, because of its relative ease of administration and favorable toxicity profile, has gained favor in situations where its cost is not a drawback. In a multicenter clinical trial involving 155 patients with advanced nsclc, treatment with paclitaxel (225 mg/m^2), as a 1-hour infusion, in combination with carboplatin (AUC=6.0), produced an overall RR of 37%, a 1-year survival of 40%, and a 2-year actuarial survival of 18% (Hainsworth JD, Chemotherapy Foundation Symposium XVI, Nov 11-13, 1998, Abs. 76:92-93). However, despite large clinical trials, the survival benefit of any of these platinum combination regimens has not been established.

To assess the impact of four novel platinum-based combinations, a randomized phase III clinical trial (E1594) was initiated by ECOG in October 1996, with an accrual goal of 1,200 patients with histologically confirmed Stage IIIb/IV nsclc. This trial was based on results of ECOG study E5592 which indicated that there is a survival advantage in combining paclitaxel, administered as a 24-hour infusion, with cisplatin when compared to the standard combination of cisplatin plus etoposide. The following regimens were repeated every 21 days except for arm 2 which was a 28-day regimen:

- arm 1: paclitaxel (135 mg/m^2) was administered over 24 hours on day 1, followed by cisplatin (75 mg/m^2)
- arm 2: cisplatin (100 mg/m^2) was administered on day 1, and gemcitabine (1 mg/m^2) was administered on days 1, 8, 15
- arm 3: cisplatin (75 mg/m^2) was administered on day 1 and docetaxel (75 mg/m^2) on day 1
- arm 4: paclitaxel (225 mg/m^2) was administered in combination with carboplatin (AUC=6), on day 1

Accrual of patients with ECOG performance status (PS) 2 was stopped on August 18, 1997, after a total of 66 patients (64 eligible for response/survival, and 61 with toxicity data) were entered, because of unexpected high incidence of Grade 4/5 toxicities in the cisplatin combinations (66%-73% of all treated) and 28% in the carboplatin arm (David H. Johnson, etal, ASCO99, Abs. 1779:461a).

In a randomized, multicenter, phase III clinical trial, among 408 eligible patients with untreated advanced nsclc, 207 were randomly assigned to paclitaxel (225 mg/m^2), over 3 hours on day 1, and carboplatin (AUC=6), on day 1, every 21 days, and 201 patients were assigned to cisplatin (100 mg/m^2) on day 1, and vinorelbine (25 mg/m^2), weekly, every 28 days. Among 184/207 patients on paclitaxel/carboplatin and 181/201 patients on vinorelbine/cisplatin, RR was similar with 27% PR, while 36% of patients survived for one year with time to progression being 8 months. These results duplicated those obtained in Southwest Oncology Group (SWOG; San Antonio, TX) study 9308. However, hematologic toxicity and nausea were higher in those treated with the vinorelbine/cisplatin combination, while peripheral neuropathy was higher with the paclitaxel/carboplatin regimen. Also, more patients in the vinorelbine/cisplatin group were unable to complete therapy as planned because of toxicity. Quality of life (QoL) was maintained in about 60% of all patients irrespective of regimen (Kelly K, etal, ASCO99, Abs. 1777:461a).

Paclitaxel, in combination with carboplatin was effective in Stage Ib, II and selected IIIa (T2N0, T1-2N1, T3N0-1) nsclc where 5-year survival rates following surgical resec-

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Exhibit 8
Selected Topoisomerase I (Topo I) Inhibitors in Development

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status➢ Location ❑ Indication(s)
AVAX Technologies ❑ Rutgers U		Topo I inhibitor	IND (f2/99)➢USA ❑ solid tumors
Banyu	NB-506	Indolocarbazole derivative, topo I inhibitor ❑ infusion	Phase I/II (o7/99)➢Japan ❑ solid tumors
Banyu ❑ Merck (Japan)	J-107088	New derivative of NB-506; induces single-strand DNA cleavage only in the presence of topo I (top1) more effectively than NB-506 or camptothecin ❑ infusion	Preclin (o7/99)➢Japan ❑ solid tumors
Biomeasure (Institut Henri Beaufour)	BN-80915	Camptothecin derivative; inhibits topo I-mediated DNA relaxation and growth of 13 tumor cell lines with a better potency than SN38 and topotecan ❑ IV, PO	Phase I (o9/99)➢USA ❑ solid tumors
BioNumerik Pharmaceuticals	Karenitecins ❑ BNP1350 ❑ Karenitecan	Highly lipophilic, silicon-containing, semi-synthetic camptothecin derivatives ❑ PO, parenteral	Phase I (o4/99)➢USA ❑ solid tumors
BTG ❑ Imperial Cancer Research Fund (ICRF)	NU/BU	Camptothecin analogs related to NU/ICRF 505, NU/ICRF 505/M and NU/ICRF 506	Preclin (o9/99)➢UK ❑ solid tumors
Cell Therapeutics ❑ M. D. Anderson Cancer Center	PG-Camptothecin Polymer	Formulation of camptothecin in a polyglutamate carrier to make it water soluble ❑ IV	Preclin (9/99)➢USA ❑ colon cancer
Daiichi Pharmaceutical	DX-8951f	Synthetic water soluble camptothecin analog more potent and with a broader spectrum of antitumor activity than other topo I inhibitors ❑ injection	Phase I (o5/99)➢USA, Europe ❑ advanced, refractory solid tumors; preclin (o5/99)➢USA ❑ pediatric solid tumors
Glaxo Wellcome	GG211; GI147211C ❑ Lurtotecan	Novel water soluble semisynthetic camptothecin analog ❑ IV	Phase I/II (o3/99)➢Europe ❑ solid tumors, breast cancer; phase II (5/97)➢Europe ❑ relapsed ovarian cancer; phase II (o3/98)➢Europe ❑ sclc
Glycosyn Pharmaceuticals	Camptothecin ❑ HAR7	7-(hydroxymethyl) camptothecin analogs (HAR) ❑ IV	Preclin (9/99)➢USA ❑ lung cancer and prostate cancer
Imperial Cancer Research Fund (ICRF)	NU/ICRF 505 and NU/ICRF 505/M (metabolite of NU/ICRF 505)	Tyrosine conjugate of anthraquinone modified at the C terminus of the amino acid as an ethyl ester ❑ IV	Preclin (9/99) ➢UK ❑ solid tumors
Imperial Cancer Research Fund (ICRF)	NU/ICRF 506	Natural product extract; topo I and II inhibitor ❑ IV	Preclin (10/96)➢UK ❑ ovarian cancer
Inex Pharmaceuticals	Formulation of topotecan ❑ TCS topotecan	Topotecan encapsulated drugs in a lipid envelope ❑ IV	Research (o7/99)➢Canada ❑ solid tumors
Matrix Pharmaceutical	Camptothecin ❑ MPI 5019	Anhydrous Vehicle Delivery (ADV) camptothecin system ❑ intratumoral	Preclin (1/99)➢USA ❑ cancer
NeXstar (Gilead Sciences) ❑ Glaxo Wellcome	NX-211	Liposomal formulation of GI147211C (Lurtotecan), a camptothecin derivative and topo I inhibitor ❑ IV	Phase I (o7/99)➢Netherlands, Canada, USA ❑ advanced solid tumors
Pharmacia & Upjohn	Methoxymorpholinyl doxorubicin (MMDX) ❑ PNU152243	Morpholinyl analog of doxorubicin, topo I and II inhibitor; predominantly inhibitor of topo I ❑ IV	Phase I/II (o3/98)➢ ❑ ovarian cancer

— *continued on next page*

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PharmaMar	Ecteinascidin 743 ❑ Et743	Tetrahydroisoquinolone alkaloid, a novel marine compound derived from the tunicate *Ecteinascidia turbinata*; a DNA minor groove, guanine-specific interacting agent that also targets topo I, inducing topo I-mediated protein-linked DNA breaks ❑ intermittent or continuous IV	Phase I (b10/96, c97, o5/99)➢USA, Scotland, the Netherlands, and France; phase II (o99)➢USA, Europe ❑ advanced, refractory solid tumors
Pierre Fabre Oncologie	F 11782	Ethylidene glucoside ester of epidophyllotoxin; novel catalytic dual inhibitor of topo I and II ❑ IV, IP, PO	Preclin (o4/99)➢France ❑ solid tumors
Rhône-Poulenc Rorer (RPR) ❑ Ilex Oncology	Intoplicine ❑ RP60475	A synthetic anticancer agent, 7H-benzo[e]pyrido[4,3-b]indole derivative which interacts with both topo I and II ❑ continuous IV	Phase I (o2/99)➢USA, Canada ❑ metastatic, refractory solid tumors
Stehlin Foundation for Cancer Research ❑ U Kentucky, NCI, U Pittsburgh, New York U		Novel highly water-soluble camptothecin analogs loaded into liposomes ❑ IV	Preclin (5/99)➢USA ❑ solid tumors
SuperGen ❑ Stehlin Foundation for Cancer Research	9-nitro-20-(S)-camptothecin (9-NC) ❑ RFS2000 ❑ Rubitecan	A third-generation topo I inhibitor; causes single-strand breaks in the DNA of rapidly dividing tumor cells; a patented analogue of camptothecin ❑ PO	Phase II (c1/99)➢USA ❑ ovarian cancer; phase II (o7/99)➢USA and phase I (o1/99)➢USA (in combination) ❑ solid tumors; phase II (o7/99)➢USA ❑ melanoma, colorectal cancer and prostate cancer; phase III (o7/99)➢USA ❑ advanced pancreatic cancer; phase II (b5/99)➢USA ❑ myelodysplastic syndrome, phase I (o7/99)➢USA ❑ nsclc
SuperGen ❑ Stehlin Foundation for Cancer Research	Liposomal 9-NC	Liposomal formulation ❑ injection	Preclin (3/99)➢USA ❑ solid tumors
Taiho Pharmaceutical (Otsuka) ❑ SRI	TAS-103	Novel quinoline derivative that targets topo I and II ❑ IV	Phase I (b10/96, o5/99)➢USA ❑ refractory solid tumors
Xenova	DACA ❑ XR5000	Novel synthetic anticancer; topoisomerase I and II inhibitor ❑ IV	Phase II (suspended 8/97)➢USA ❑ solid tumor; phase II (o8/99)➢ Europe ❑ refractory solid tumors
Xenova ❑ Auckland Cancer Research Laboratory	XR5942 series	Orally available topo I inhibitors; second generation XR5000 ❑ PO	Preclin (o5/99)➢UK ❑ solid tumors
Xenova Group	Bis-phenazine ❑ XR5944	Novel bis-phenazine; A topo I and II inhibitor with a preference for topo I ❑ IV	Research (o8/99)➢UK ❑ solid tumors

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

tion range from 38% to 9%. Although adjuvant therapies have shown little if any survival benefit, an induction regimen consisting of perioperative paclitaxel and carboplatin was shown effective in resectable early-stage nsclc. According to preliminary results from a completed phase II clinical trial, conducted by the Bimodality Lung Oncology Team (BLOT), induction chemotherapy was feasible without compromising surgery, and yielded high RRs.

Between June 1997 and July 1998, the trial enrolled 94 patients with clinical Stage T2N0 (n=45), T1N1 (n=1), T2N1 (n=26), T3N0 (n=17), T3N1 (n=5) disease who were treated perioperatively with paclitaxel (225 mg/m^2) as a 3-hour infusion, and carboplatin (AUC=6), administered every 21 days, for two cycles before, and three cycles after surgery, in those who underwent complete resection.

Of the 92 patients with resectable disease, 83 (90%) were explored and 75 (82%) were completely resected. There were 4 (4%) pathologic CR and 3 deaths, one during induction chemotherapy and 2 postoperatively. Most importantly, no increased or unexpected toxicity, or surgical morbidity were observed (Pisters KMW, etal, ASCO99, Abs. 1800:467a). A randomized intergroup trial comparing

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3 cycles of paclitaxel and carboplatin induction chemotherapy with surgery, to surgery alone, in early-stage nsclc, is in the works.

Data from a large-scale, phase III clinical trial, conducted by SWOG between April 1996 and January 1998, proved that paclitaxel with carboplatin, and vinorelbine with cisplatin, provide comparably effective palliation in patients with untreated advanced nsclc, but the paclitaxel/carboplatin combination resulted in a more favorable toxicity profile, and better tolerability and compliance.

A phase III randomized, parallel, open label, multicenter clinical trial (protocol IDs: RP-56976-TAX-326, RP-56976-V-326) of docetaxel plus cisplatin, or docetaxel plus carboplatin, versus vinorelbine plus cisplatin, in chemotherapy-naive patients with unresectable nsclc (Stage IIIb, Stage IV, or recurrent disease) was initiated in July 1998 to accrue 1,080 patients (360 per arm) within 18 months. The trial will compare the two docetaxel and platinum drug combinations to the standard regimen of vinorelbine and cisplatin in terms of overall survival, time to progression, overall objective RR, duration of responses, safety and QoL.

Patients are randomly assigned to one of the following treatments regimens:

- arm I: IV docetaxel administered over 1 hour, immediately followed by IV cisplatin over 1 hour, repeated every 21 days
- Arm II: IV docetaxel administered over 1 hour, immediately followed by IV carboplatin over 1 hour, repeated every 21 days.
- Arm III: IV vinorelbine administered over 6-10 minutes on days 1, 8, 15, and 22 with IV cisplatin administered on day 1 only, following vinorelbine; courses are repeated every 28 days.

Treatment in all arms continues for 6 courses in the absence of unacceptable toxicity or disease progression. After completion of the 6 treatment courses, patients may continue on their randomized treatment regimen at the discretion of the treating physician. QoL is assessed before every treatment course, and then every 2 months until death, and patients are followed every 2 months until death.

Two-drug combination regimens have also paired vinorelbine, a drug approved for the treatment of advanced nsclc, with either a taxane, or gemcitabine. Vinorelbine is active against nsclc with a >20% single-agent RR.

Vinorelbine is being effectively used to enhance the effectiveness of docetaxel in a combination regimen with dose-dense docetaxel, and prophylactic granulocyte-colony stimulating factor (G-CSF). In a phase I trial, this regimen showed additive or synergistic effects (Miller VA, etal, ASCO98, Abs. 1813:471a). Although these two agents act by a different mechanism on tubulins, both promote apoptosis by phosphorylating and inactivating bcl-2. These two drugs when administered simultaneously in *in vivo* and *in vitro* models, exhibited additive or synergistic effects.

In a phase II clinical trial, conducted at Memorial Sloan-Kettering Cancer Center (New York, NY), the efficacy and safety of this combination was tested in 35 chemotherapynaive patients with advanced nsclc (Stage IV=91%). The protocol consisted of vinorelbine (45 mg/m^2) administered by IV push, followed by docetaxel (60 mg/m^2) infused over one hour, administered every two weeks with subcutaneous G-CSF (5 mg/kg), on days 3-12. Supportive therapies included oral dexamethasone (8 mg), twice daily, for five doses, starting 24 hours before docetaxel infusion, and oral ciprofloxacin (500 mg), twice daily, on days 3-9. The median number of cycles administered was 10 (range = 2 to 27).

Among evaluable patients PR was reported in 19/35 (54%) of treated patients. Median duration of response was 6+ months (range=4 to 16+ months) and the predicted one-year survival after a median follow-up of 7 months was 86%. With regard to the safety profile, while there was no Grade 3/4 neuropathy, thrombocytopenia, or vomiting, other toxicities included neutropenic fever (23%), dyspnea/infiltrates (34%), onycholysis (43%), and lacrimation (77%). Because of cumulative adverse effects, application of this regimen for a shorter period, such as in a neoadjuvant setting, may provide optimal benefit while minimizing toxicity (Krug LM, etal, ASCO99, Abs. 1775:460a).

The combination of paclitaxel and carboplatin is a standard regimen in the treatment of advanced nsclc. Its major toxicities include myelosuppression, neuropathy and myalgias/arthralgias. The definitive role of the use of amifostine with this regimen awaits completion of a NCI-sponsored phase III open label randomized clinical trial (protocol ID: RTOG-9801) of amifostine mucosal protection in patients with favorable performance inoperable Stage II, IIIa, or IIIb nsclc, treated with sequential induction and concurrent hyperfractioned RT with paclitaxel and carboplatin, that was initiated in September 1998 by the Radiation Treatment Oncology Group (RTOG). The trial will accrue 304 chemotherapy- or RT-naive patients (152 in each arm), over 38 months, to evaluate whether the addition of amifostine can reduce the incidence and severity of nonhematologic toxicity, specifically esophagitis and pneumonitis, and its impact on QoL and symptom distress. The study will also establish the relationship of tobacco and alcohol use during treatment to QoL and symptom distress, specifically esophagitis, and evaluate the efficacy of induction therapy with paclitaxel and carboplatin, followed by concurrent chemotherapy and hyperfractionated RT, in these patients.

Patients are randomized to induction chemotherapy followed by concurrent RT and chemotherapy, with or without amifostine. Patients are administered IV paclitaxel by a 3-hour continuous infusion on days 1 and 22, and then by a 1-hour infusion, weekly, for 6 weeks, starting on day 43. IV carboplatin is administered over 30 minutes immediately after each paclitaxel dose. Filgrastim (G-CSF) is administered subcutaneously for 10-14 days after each

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of the first two paclitaxel and carboplatin doses. RT begins on day 43, and is administered twice daily, for 5 days per week, for 6 weeks. On day 43 only patients in arm I are treated with amifostine, by a 5-minute IV infusion, 4 days-per-week, for 6 weeks. QoL is assessed before treatment, before chemoradiation (post 2 courses of induction chemotherapy), the last week of chemoradiation (week 6), and at the 6-week follow-up visit. Patients are followed every 3 months for 1 year, then every 6 months for 2 years, and then annually thereafter.

In a phase II clinical trial conducted at the University of North Carolina (Chapel Hill, NC), amifostine (740 mg/m^2) was administered in the first 15 patients prior to paclitaxel (225 mg/m^2), and prior to carboplatin (AUC=6); subsequently, the second amifostine infusion prior to carboplatin was deleted. A total of 57 cycles of chemotherapy and 98 infusions of amifostine were delivered to 21 patients. Grade 3/4 toxicity, as a percent of cycles, included neutropenia (5/5), thrombocytopenia (7/2) and anemia (11/0); there was no Grade 4 nonhematologic toxicity, and 7 of 57 (12%) cycles were complicated by hospitalization with 1 hospitalization related to amifostine-induced hypotension. Of the 98 amifostine infusions, 6 were interrupted for hypotension, one by vomiting, and 26% and 24% were complicated by acute nausea and vomiting, respectively. Among 19 of 21 evaluable patients, 5% experienced CR, 36% PR, and disease stabilized in 16% and progressed in 43%. Median survival was 4.6 months with a one-year survival of 15% (Socinski MA, etal, ASCO99, Abs. 2015:523a).

Another new chemotherapeutic active in nsclc is irinotecan (CPT-11) which, in combination with cisplatin, appears to be as active, and perhaps less toxic, as other established regimens. A randomized multicenter phase III clinical trial, conducted between June 1995 and October 1997, by the CPT-11 Lung Cancer Study Group of the National Cancer Center Hospital East (Kashiwa, Chiba, Japan), compared a combination of CPT-11 and cisplatin with vindesine and cisplatin in 210 chemotherapy-naive patients with advanced nsclc (Stage IIIb=59% or IV=41%). Patients were treated with either cisplatin (80 mg/m^2) on day 1 and CPT-11 (60 mg/m^2) on days 1, 8 and 15 (regimen A=98 patients), or cisplatin (as above) and vindesine (3 mg/m^2) on days 1, 8 and 15 (regimen B=101 patients); both regimens were repeated every 4 weeks until disease progression. After a median of 2 courses, among 98 evaluable patients on regimen A, and 101 on regimen B, there were 28 (29%) and 22 (22%) objective responses, respectively. According to interim survival results on 203 eligible patients as of September 1998, median survival was 45.4 and 49.6 weeks, for regimen A and B, respectively. Grade=3 toxicities were leukopenia 39% and 58%, neutropenia 63% and 83%, and diarrhea 13% and 1%, respectively (Niho S, etal, ASCO99, Abs. 1897:492a).

The value of a cisplatin-based regimen may be finally established by a large phase III randomized clinical trial (protocol IDs: MRC-BLT, EU-98003), part of the Big Lung Trial (BLT) program sponsored by the Medical Research Council (UK), that was initiated in January 1999, to investigate the role of cisplatin-based chemotherapy in patients with any stage nsclc treated either by RT and/or surgery or no treatment. This very large trial, to be completed within 3-4 years, is to accrue patients in 4 treatment groups:

- 4,000 patients to be treated by surgery alone
- 2,500 patients to undergo surgery plus RT
- 2,000 patients to be treated with radical RT
- 800 patients to be managed by best supportive care (BSC)

The objective of the trial is to establish the value of adding cisplatin-based chemotherapy to standard treatment in terms of survival in patients with nsclc. Patients are randomized either to arm I (treatment alone) or arm II (the same treatment with chemotherapy). Chemotherapy begins within 10 weeks after surgery or radical RT, or as soon as possible after diagnosis. Patients randomized to arm II are treated with a total of 3 courses, repeated every 3 weeks, with one of the following regimens:

- A: cisplatin IV on day 1, followed by vindesine on days 1-8
- B: mitomycin, ifosfamide, and cisplatin on day 1
- C: mitomycin, vinblastine, and cisplatin on day 1
- D: vinorelbine on days 1-8, and cisplatin on day 1

Patients will be followed at 3 months, 6 months, 1 year and annually thereafter.

Shortcomings of platinum-based regimens are hematologic, renal and neurologic toxicities. Many trials are ongoing to assess the ability of amifostine to decrease such toxicities in various platinum-based drug combinations. In a randomized phase III trial of the MIP regimen in advanced poor prognosis nsclc, addition of amifostine did not prevent either acute or cumulative renal, neurologic or hematologic toxicities. Among 190 patients (Stage IIIb=50% and Stage IV=50%), the overall RR was a disappointing 29% without any difference between those treated with amifostine and controls. It is speculated that lack of efficacy of amifostine may be attributable to low numbers of performed cycles, low toxicity of this regimen, and the short median survival of patients (Souquet PJ, etal, ASCO99, Abs. 1882:488a).

Other trials showed a benefit by adding amifostine to a platinum-based regimen. A multicenter phase II clinical trial, conducted by the Italian Lung Cancer Amifostine Project, investigated a possible synergistic effect between amifostine and chemotherapy in advanced nsclc. The protocol was similar to that of the SWOG 9308 trial of cisplatin, plus vinorelbine but with the addition of IV amifostine (740 mg/m^2) on day 1, every 4 weeks, for a maximum of 6 cycles. According to the SWOG protocol, GM-CSF was also allowed in the case of Grade 4 neutropenia. Among 40 patients entered in the trial, there were 20 (50%)

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objective responses with 7 CR. Three patients with inoperable Stage IIIb disease at diagnosis underwent radical dissection (2 pathologic CR). Toxicity was manageable with a withdrawal rate of 15%. A randomized trial comparing this regimen with or without amifostine is warranted (Manzione L, etal, ASCO99, Abs. 1925:499a).

Taxane-based combinations without platinum agents are also gaining favor. Preliminary results from a 315-patient multicenter randomized phase II clinical trial, conducted by the Greek Cooperative Group for Lung Cancer, seem to indicate that a docetaxel/gemcitabine regimen has a comparable activity and toxicity profile as a docetaxel/cisplatin regimen in advanced nsclc. Chemotherapy-naive patients with Stage IIIb and IV nsclc were treated with either docetaxel (100 mg/m^2) on day 1, and cisplatin (80 mg/m^2) on day 2 (arm 1), or with gemcitabine (1100 mg/m^2) on days 1 and 8, and docetaxel (100 mg/m^2) on day 8 (arm 2); rhG-CSF (150 mg/m^2) was administered subcutaneously in arm 1 on days 3-9, and in arm 2 on days 9-15; both regimens were repeated every 3 weeks.

The probability of response with the docetaxel/cisplatin regimen was significantly higher in patients with nsclc other than adenocarcinoma, while the opposite was observed in those with adenocarcinoma. Toxicities, based on a total of 1161 cycles administered (arm 1=595 and arm 2=566) with a median of 3 and 4 cycles/patient, respectively, are summarized below (Georgoulias V, etal, ASCO99, Abs. 1778:461a).

Toxicity	Treatment Groups			
	Paclitaxel/Cisplatin (Arm 1)		Paclitaxel/Gemcitabine (Arm 2)	
	(#)	(%)	(#)	(%)
Grade 3/4				
Anemia	9	6	6	4
Neutropenia	50	33	31	22
Febrile neutropenia	24	16	20	14
Thrombocytopenia	4	3	7	5
Diarrhea	18	12	4	3
Fatigue	45	30	49	33
Grade 2/4				
Neurotoxicity	10	7	6	4

Another taxane combination, evaluated in a phase I clinical trial in advanced nsclc, involves treatment with weekly docetaxel and vinorelbine. Between May 1997 and August 1998, 21 patients (Stage IIIb=2, IV=13, recurrent=6) were treated with weekly vinorelbine (20 mg/m^2) with dexamethasone premedication, and escalated doses of docetaxel. Maximum tolerated dose (MTD) without G-CSF for docetaxel was 25 mg/m^2 per week; with G-CSF, in chemotherapy-naive patients, MTD was 35 mg/m^2 per week. Patients were assessed for response at 9 and 18 weeks. One patient died with neutropenic sepsis, and another from a multifactorial etiology. The overall PR rate was 28% with a 40% RR in previously untreated patients (Johnston E, etal, ASCO99, Abs. 1838:476a). A phase II clinical trial of another regimen of docetaxel (60 mg/m^2) plus vinorelbine (45 mg/m^2), administered every two weeks to chemotherapy-naive patients with Stage IIIb/IV nsclc, is ongoing at Memorial Sloan-Kettering Cancer Center, based on results from a phase I clinical trial (Kris MG, etal, Chemotherapy Foundation Symposium XVI, Nov 11-13, 1998, Abs. 53:63-64).

A phase II clinical trial of docetaxel and CPT-11 in recurrent or metastatic nsclc, to enroll 44 patients within 24 months, is also being planned by the North Central Cancer Treatment Group (protocol ID: NCCTG-982453). The protocol involves sequentially administered IV CPT-11 over 90 minutes, immediately followed by IV docetaxel over 60 minutes on day 1, repeated every 3 weeks, for 6 courses, in the absence of disease progression or unacceptable toxicity. Patients will be followed every 3 months for 5 years or until death.

An open label, two-stage, phase II clinical trial of paclitaxel and vinorelbine as first-line chemotherapy in the treatment of Stage IIIb or IV nsclc is also being conducted by the Grupo Oncologico Cooperativo del Sur (protocol IDs: GOCS-01-LC-97, NCI-V97-1274). Each treatment cycle, repeated every 28 days, involves vinorelbine, administered by slow IV infusion on days 1 and 8, and paclitaxel, by continuous 3-hour infusion, on day 1. Patients are assessed for response after 2 cycles in the absence of unacceptable toxicity, and treatment is discontinued if there is evidence of progressive disease. Patients are followed each month until death.

Other combinations involve drugs found effective as single agents in nsclc such as vinorelbine and gemcitabine. Gemcitabine, alone or in combination with cisplatin has been approved for the treatment of locally-advanced or metastatic nsclc. As is the case with vinorelbine, RRs of nsclc patients treated with gemcitabine exceed 20%. Because of its activity, it is being paired with agents other than platinum drugs, in the hopes of creating more efficacious and less toxic treatment options. A combination regimen of gemcitabine and vinorelbine, administered weekly at near full doses of each drug, either as first- or second-line treatment, is also active and reasonably well tolerated in patients with nsclc.

In a multicenter phase II clinical trial, conducted by the Minnie Pearl Cancer Research Network between January and September 1998, the feasibility and efficacy of a gemcitabine/vinorelbine combination as second-line treatment of nsclc was evaluated in 36 patients whose disease had progressed after one previous chemotherapy regimen. Treatment involved IV vinorelbine (20 mg/m^2) followed by IV gemcitabine (1000 mg/m^2), on days 1, 8, and 15, repeated every 28 days. Patients were previously treated with a taxane (n=1), a platinum agent (n=4), or both (n=31). Of these, 15 (42%) had experienced a previous objective response to treatment. Among evaluable patients,

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there were 7 (21%) objective responses (PR=6 and CR=1), and 15 (45%) minor responses/stable disease; 13 patients remained progression-free after a median follow-up of 4 months. Grade 3/4 toxicity included leukopenia (25%), anemia (22%), thrombocytopenia (19%), fever (19%), and fatigue (16%); there was one (3%) septic death. This combination is currently being evaluated as first-line therapy (Gian V, ASCO99, Abs. 1949:505a).

Based on preclinical and prior phase I studies, a phase II clinical trial of weekly gemcitabine and vinorelbine was carried out in patients with nsclc at M. D. Anderson Cancer Center (Houston, TX). Between November 1997 and November 1998, 56 nsclc patients (30 previously treated and 26 untreated) were administered vinorelbine (900 mg/m^2), as a bolus, and gemcitabine (25 mg/m^2), as a 30-minute infusion, sequentially, on days 1, 8, and 15, of a 28-day cycle.

Among 19 evaluable previously untreated patients, there were 8 (42%) PR, and disease stabilization or minor responses occurred in 7 (37%), and disease progressed in 4 (21%). Median survival had not yet been determined at the time these results were presented. Primary toxicity in this group was myelosuppression, causing 35 of 199 (18%) intended doses of drug to be held back or reduced. Among the first 26 evaluable previously treated patients, there were 3 (12%) PR, 12 (46%) minor responses, and disease progressed in 11 (42%). Median survival of this group at 32.4 weeks compares favorably with historical controls. Here, also, the main toxicity was myelosuppression causing 33 of 184 (18%) intended doses of drug to be held back or reduced. In both groups, 20% of patients developed <Grade 2 phlebitis. Investigators suggest that this regimen be evaluated against platinum-containing combination therapies (Herbst RS, etal, ASCO99, Abs. 1782:462a).

In a phase II clinical trial, conducted by the Austrian Association for the Study of Lung Cancer (AASLC) at the University of Vienna, 70 chemotherapy-naive patients with advanced nsclc (Stage IIIb=19%, Stage IV=81%) were treated with vinorelbine (25 mg/m^2), administered as a 10-minute IV infusion, followed by gemcitabine (1200 mg/m^2), as a 30-minute infusion, on days 1, 8 and 15. Standard antiemetics were used but no prophylactic hematopoetic growth factors. The treatment cycle was repeated every 4 weeks up to a total of 8 cycles unless there was an indication of progressive disease. Among 60 patients evaluable for response, PR, stable disease and progressive disease were seen in 19%, 34% and 33%, respectively, and median overall survival was 9 months. Among 33 patients evaluable for toxicity, Grade 3/4 neutropenia occurred in 55%, anemia in 12% and thrombocytopenia in 15%. Non-hematologic toxicities including nausea, flu-like symptoms, thrombophlebitis and elevation of liver enzymes, were mild (Pirker R, etal, ASCO99, Abs. 1849:479a).

According to results from a phase II clinical trial using a similar treatment protocol, that enrolled 33 patients with advanced nsclc (Stage IIIb=4, Stage IV=23, recurrent=5) from May 1997 to April 1998, among 24 evaluable patients there were 7 (29%) PR and disease stabilized in 14 and progressed in 3. There was no Grade 3/4 nonhematologic toxicity but there were two episodes of febrile neutropenia, one death from neutropenic sepsis, and 3 patients required dose reduction because of hematologic toxicity (Lilenbaum RC, etal, Chemotherapy Foundation Symposium XVI, Nov 11-13, 1998, Abs. 54:64).

In another phase II clinical trial involving a weekly combination of gemcitabine (25 mg/m^2) and vinorelbine (900 mg/m^2), administered on days 1, 8, and 15 of a 28-day cycle in patients with Stage IIIb/IV nsclc, among 57 patients, 3 (5%) developed pneumocystis carinii pneumonia (PCP). One patient was successfully treated while the other two died as a result of this complication (Blumenschein GR Jr, etal, ASCO99, Abs. 1919:497a).

Monochemotherapies

Monochemotherapy is rarely used as first-line treatment in any stage of nsclc. Single-drug therapies using such agents as paclitaxel, docetaxel, gemcitabine, vinorelbine, or ifosfamide, are mostly used as second- or third-line treatment of advanced nsclc after failure of multimodality or combination therapies.

Docetaxel, which is actively investigated in various combination regimens in nsclc as initial chemotherapy, is also used alone as second-line therapy in patients who failed prior platinum-based chemotherapy. Docetaxel offers significantly greater clinically meaningful benefits with manageable toxicity when compared to vinorelbine or ifosfamide, agents commonly used in this setting. According to phase III clinical trials conducted at Memorial Sloan-Kettering Cancer Center, docetaxel achieved the highest RR of any other regimen, and exhibited comparable survival rates with that of platinum-containing regimens.

To establish the role of docetaxel as second-line therapy in platinum-refractory nsclc, a multicenter (23-site) phase III clinical trial was undertaken to compare two different doses of docetaxel with the standard vinorelbine or ifosfamide regimen. The trial randomized 373 patients to docetaxel (75 mg/m^2 or 100 mg/m^2), every 3 weeks, or vinorelbine (30 mg/m^2) weekly, or ifosfamide (2 g/m^2), daily, for 3 days, every 3 weeks. Baseline demographics were similar in all three treatment arms.

At trial completion, 350 patients were evaluable. RRs were 12% for docetaxel at 100 mg/m^2, 8% for docetaxel at 100 mg/m^2, and 1% for either ifosfamide or vinorelbine. Time-to-progression (TTP) was longer with docetaxel. While median survival of 5.6 months was the same in all three groups, among the 2/3 of patients who were not treated with additional chemotherapy upon failure of the current regimen, the one-year survival rate of 32% was significantly higher in patients treated with docetaxel, compared to either vinorelbine or ifosfamide (10%). Furthermore, QoL analysis showed a significant trend favoring either dose

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Exhibit 9
Selected Thymidylate Synthase Inhibitors and Related Agents in Development

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status➢ Location ❑ Indication(s)
AstraZeneca	ZD9331	TS inhibitor ❑ IV	Phase II (o6/98)➢USA, Europe ❑ solid tumors
Agouron Pharmaceuticals (Warner-Lambert)	AG2034	Inhibitor of the enzyme glycinamide ribonucleotide formyltransferase (GARFT) ❑ IV	Phase I (c6/98)➢USA ❑ solid tumors
BioNumerik Pharmaceuticals	MDAM	Patented nonpolyglutamylatable antifolate ❑ IV, PO	Phase I (o2/99)➢USA ❑ solid tumors
Eli Lilly	LY 231514	Multi-targeted antifolate (MTA) that inhibits multiple enzymes, involved in the purine and pyrimidine biosynthesis pathways; potently inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), GARFT and other folate-dependent enzymes ❑ IV	Phase III (o1/99)➢USA, Australia ❑ nsclc; phase II (o5/99)➢USA ❑ advanced solid tumors, mesothelioma; phase II (c98)➢USA ❑ advanced colorectal cancer; phase II (c98)➢England ❑ locally recurrent or metastatic breast cancer; phase I (c98)➢Europe ❑ metastatic renal cancer; phase I (o5/99) ❑ squamous cell carcinoma of the head and neck; phase II (o5/98)➢Spain ❑ metastatic transitional cell bladder cancer; phase II (o97)➢USA ❑ pancreatic cancer
Eli Lilly	LY309887	Potent GARFT inhibitor that catalyzes the first two folate-dependent steps of de novo purine biosynthesis; reduced analog of folic acid ❑ IV	Phase I (c98)➢USA ❑ solid tumors
Glaxo Wellcome	Eniluracil ❑ GW776C85, 776C	A uracil analog, mechanism-based inactivator of dihydropyrimidine dehydrogenase (DPD), the rate limiting enzyme in 5-FU catabolism ❑ PO	Phase II (o3/98)➢USA ❑ refractory breast cancer; phase III (o3/98)➢USA ❑ untreated colorectal cancer, advanced pancreatic cancer; phase I (o3/98)➢USA ❑ recurrent or advanced head and neck cancer; phase II (b7/98)➢USA ❑ skin cancer, Merkel cell carcinoma
Ilex Oncology ❑ MPI Research	Piritrexim	DHFR inhibitor that enters cells by passive diffusion and inhibits DNA synthesis ❑ injection, PO, topical	Phase II (discontinued 10/98)➢USA ❑ advanced bladder cancer; phase II (o3/99)➢USA ❑ malignant fibrous histiocytoma
Ilex Oncology	Aminopterin	An antifolate, inhibits both the DHFR and folic acid synthesis ❑ injection	Phase II (o3/99)➢USA ❑ acute lymphoblastic leukemia (ALL); phase II (o7/99)➢USA ❑ persistent, recurrent or refractory endometrial cancer
Kyowa Hakko Kogyo ❑ NCI	UCN-01	Staurosporine analog; protein kinase C inhibitor that may block G2 arrest of the cell cycle following DNA damage; also acts on cell cycle-dependent mechanisms, such as induction of expression of p21 protein, and inhibition of cyclin-dependent Rb kinases ❑ IV	Phase I (o5/99)➢USA, Japan ❑ solid tumors
Otsuka Pharmaceutical	Emitefur ❑ BOF-A2	Novel formulation composed of 1-ethoxymethyl 5-FU (EM-FU), a slow release form of 5-FU, and 3-cyano-2,6,-dihydropyrimidine, which inhibits 5-FU degradation ❑ IV	NDA (f97)➢Japan ❑ solid tumors

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Sparta Pharmaceuticals (SuperGen) ❑ Dana-Farber Cancer Institute	PT-523	Folate antagonist; more lipid soluble than MTX to cross cell membranes ❑ IV	Preclin (o4/99)➢USA, The Netherlands ❑ solid tumors
Taiho Pharmaceutical (Otsuka) ❑ Bristol-Myers Squibb	S-1	TS inhibitor ❑ PO	Phase II➢Japan; phase I➢Europe ❑ solid tumors
Taiho Pharmaceutical (Otsuka) ❑ Kagoshima U, Osaka U Medical School	5-fluoro2'-deoxyuridine (FdUrd)	A fluorinated pyrimidine that is cytotoxic to cells as a consequence of generation of 5-fluoro-2'-deoxyuridylate (FdUMP), a mechanism-based inhibitor of TS ❑ intrathecal, intratumoral	Phase I/II (b1/96)➢Japan ❑ neoplastic meningitis; phase II (1/97)➢ USA ❑ hepatobiliary cancer
Zarix ❑ Hoffmann-La Roche (discontinued), Agouron Pharmaceuticals (Warner-Lambert)	Nolatrexed dihydrochloride ❑ AG337 ❑ Thymitaq	Nonclassical antifolate; direct TS inhibitor kills tumorcells by inducing apoptosis ❑ IV, PO, intraperitoneal, intramuscular	Phase II (c8/99)➢USA ❑ hepatocellular carcinoma; phase II/III (b6/97)➢ USA, Europe ❑ head and neck cancer; phase II (12/97)➢USA ❑ colorectal cancer; phase II (PO) (o7/97) UK ❑ solid tumors, lung cancer, pancreatic cancer, prostate cancer; phase I (PO) (o1/99)➢USA UK ❑ solid tumors; phase I (IV) (o1/99)➢USA ❑ solid tumors

Source: NEW MEDICINE Oncology KnowledgeBASE (∩m|OK), September 1999

of docetaxel, with several of the differences being statistically significant. Also, PR rates were 11.9% with docetaxel 100 mg/m^2, 7.5% with docetaxel 75 mg/m^2, and 1% with ifosfamide or vinorelbine. Incidence of Grade 4 neutropenia/infection were 77%/12% in the 100 mg/m^2 docetaxel group, 53%/7% in the 75 mg/m^2 docetaxel group, and 30%/1% in the ifosfamide, or vinorelbine group (Fossella F, etal, ASCO99, Abs. 1776:460a and Miller VA, etal, ASCO99, Abs. 1895:491a).

QoL of docetaxel versus BSC in patients with nsclc previously treated with platinum-based chemotherapy, was assessed in an international, randomized, multicenter phase III clinical trial involving 204 patients with nsclc. Patients were randomized to docetaxel (100 mg/m^2=49 and 75 mg/m^2=55) or BSC (100). Among 196 evaluable patients, 158 (81%) had Stage IV disease, and 49 (25%) were exposed to 2 prior chemotherapy regimens. Based on Lung Cancer Symptom Scale (LCSS) data, an analysis of covariance on changes from baseline to last assessment showed benefits for docetaxel compared to BSC in patient-rated pain and overall QoL and observer-rated total score, appetite and fatigue (Dancey J, etal, ASCO99, Abs. 1896:491a).

Paclitaxel, as first-line therapy, administered on a weekly schedule, is associated with diminished toxicity, allows enhanced dose-intensity, yields preliminary outcome data comparable to combination therapy, and may be more active than conventional schedules in advanced nsclc. To evaluate the efficacy and toxicity of weekly paclitaxel at maximum dose-density, a phase II clinical trial (CALGB 9731) was undertaken that enrolled 39 patients with chemotherapy-naive Stage IIIb (n=22) and Stage IV (n=5) nsclc. Paclitaxel (150 mg/m^2) was administered as a weekly 3-hour infusion, for six weeks of each eight week cycle with standard anaphylaxis prophylaxis. According to preliminary data, based on 36 patients, there were 14 PR (39%). Median survival had not been reached at a median follow-up >6 months. Grade 3/4 hematologic toxicities were seen in 33% of patients with no toxic deaths. Nonhematologic toxicities included Grade 2 neuropathy (28%), Grade 3 neuropathy (28%), and Grade 3 hyperglycemia (32%) (Akerley W, etal, ASCO99, Abs. 1783:462a).

Paclitaxel with and without carboplatin in advanced nsclc (Stage IIIb, IV or recurrent disease) is being investigated in an NCI-sponsored phase III clinical trial (protocol ID: CLB-9730) initiated in October 1997 by the Cancer and Leukemia Group B, that is to accrue 600 chemotherapy-naive patients over 2 years. The objectives of this trial are to compare, overall survival, QoL, RR and toxicity of the two regimens. Patients are randomized either to arm I to be treated with IV paclitaxel over 3 hours on day 1 of each course, or arm II to be treated with paclitaxel as in arm I, followed by IV carboplatin over 1 hour. In the absence of tumor progression or unacceptable toxicity, treatment is repeated every 21 days for 6 courses. QoL assessments are conducted before treatment and at 2, 6, 9, and 12 months, and patients are followed every 3 months for 2 years, then every 6 months until disease progression or death.

It also appears that paclitaxel activity is not decreased in nsclc with p53 mutations, as is the case with platinum agents. *In vitro* data, and animal studies, suggest that paclitaxel may have a unique ability to activate tumor cell apop-

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tosis in the absence of wild-type p53. For instance, response to paclitaxel and concurrent radiation is not affected by p53 mutations. In order to determine whether p53 mutations affect response to single-agent paclitaxel in nsclc, tumor tissue was obtained from 25 patients with metastatic nsclc who participated in studies of weekly paclitaxel (150-175 mg/m^2), conducted by the Brown University (Providence, RI) Oncology Group. Mutations were found in 7/25 (28%) patients, including 5 patients with an exon 5 mutation, and 2 with an exon 7 mutation. RRs of 71% for tumors with p53 mutations and 56% for tumors with wild-type p53, did not differ significantly. The 1-year survival for tumors with and without p53 mutations was 38% in both cases (King T, etal, ASCO99, Abs. 1973:511a).

Vinorelbine monotherapy was compared to two combination regimens, vinorelbine and cisplatin or vindesine and cisplatin in a European multicenter randomized clinical trial, that enrolled 612 patients from June 1989 to May 1991. The regimens consisted of vinorelbine (30 mg/m^2), weekly, vinorelbine and cisplatin (120mg/m^2) on day 1 and day 29, and then every 6 weeks, and cisplatin and vindesine (3 mg/m^2), weekly, for 6 weeks, and then every other week. There was a significant advantage in RR and survival for the vinorelbine and cisplatin arm when compared to the two others. After a six year follow-up, the significant superiority of this arm was confirmed. Further analysis by prognostic factors showed that the advantage of the vinorelbine and cisplatin arm was concentrated in PS 0-1 patients with a median survival of 43 weeks and a 1-year survival rate of 38% versus respectively 36 weeks and 31% for vinorelbine alone and 34 weeks and 29% for cisplatin and vindesine. PS 2 patients experienced a similar survival (median=20 weeks) whatever the treatment. Active single agents such as vinorelbine should, therefore, be considered as appropriate alternatives in PS 2 patients with inoperable nsclc who do not derive a survival benefit from platinum-based combination regimens (Soria JC, etal, ASCO99, Abs. 1893:491a).

Irinotecan (CPT-11), has shown a 32% RR as a single agent, and a 52% RR in combination with cisplatin in advanced nsclc. The performance of single-agent CPT-11 in advanced nsclc was evaluated in a large, randomized, multicenter, phase III clinical trial, conducted by the CPT-11 Lung Cancer Study Group West at Osaka Prefectural Habikino Hospital, in Japan, that compared two combination regimens of cisplatin and CPT-11, or cisplatin and vindesine, with single-agent CPT-11. Between July 1995 and January 1998, 398 chemotherapy-naive patients with advanced nsclc were randomly assigned to cisplatin (80 mg/m^2) on day 1 and CPT-11 (60 mg/m^2) on days 1, 8, 15 (arm A); or cisplatin (as above) and vindesine (3 mg/m^2) on days 1, 8, 15 (arm B); or single-agent CPT-11 (100 mg/m^2) on days 1, 8, 15 (arm C). Among 378 evaluable patients (Stage IIIb=37% and Stage IV=63%) for response, toxicity and survival, objective responses were observed in 55 (43%), 38 (31%) and 26 (21%) patients in arms A, B and C, respectively. Grade 4 neutropenia occurred in 36.2%, 53.2% and 7.9% of patients, respectively, and Grade 3 or worse diarrhea was observed in 12.6%, 4.0% and 15.0%, respectively. There was 1 treatment-related death in arm B and C. As of September 30, 1998, median survival was 50.3 weeks, 47.4 weeks and 46.1 weeks, and 1-year survival rate was 47.5%, 37.9% and 40.7%, in arms A, B and C, respectively (Masuda N, etal, ASCO99, Abs. 1774:459a).

Multidrug Regimens in Advanced Disease

Three-drug platinum-containing regimens reportedly produce objective responses in 30%-60% of patients with advanced nsclc. Because docetaxel was shown to produce objective responses in 20%-35% of such patients, a phase I/II clinical trial of escalating doses of docetaxel, ifosfamide and cisplatin (TIC) was undertaken by the Irish Clinical Oncology Research Group (ICORG; Dublin, Ireland) to establish the dose limiting toxicity (DLT) in conjunction with lenograstim support, in patients with Stage III/IV nsclc. MDT of TIC was established at 75 mg/m^2, 3000 mg/m^2 and 75 mg/m^2, respectively, with lenograstim support, and will be evaluated in a phase III clinical trial (Crown JP, etal, ASCO99, Abs. 1840:477a).

A 3-drug combination involving paclitaxel, carboplatin, and CPT-11, was tested in a multicenter, phase I clinical trial that enrolled 32 patients with advanced or metastatic nsclc. MTD occurred at a paclitaxel dose of 175 mg/m^2, infused over 3 hours, in combination with carboplatin (AUC=5) over 0.5 hours, and CPT-11 (100 mg/m^2) over 1.5 hours, administered on day 1, every 3 weeks. DLT was Grade 4 diarrhea, Grade 3 neuropathy, and Grade 4 neutropenia/infection. Among 31 patients evaluable for response, the objective RR was 64.5% with 3 CR (9.7%), 17 PR (54.8%), and 3 minor responses (9.7%); disease stabilized in 5 (16.1%) and progressed in 3 (9.7%). There was a rapid cavitation in primary lesions. Median time-to-tumor progression was 7.1 months (range=0.7 to 23.3) and median survival was 16.1 months (range=1.3 to 23.3). The 1-year survival rate was 55.6%. This regimen was also evaluated in a phase II clinical trial that enrolled 35 patients with advanced nsclc (Stage IIIb=10 and Stage IV=25). Grade 3/4 toxicities at MTD were neutropenic fever (n=10), neutropenia without fever (n=4), diarrhea (n=3), nausea/vomiting (n=3); and neurotoxicity (n=1). There was 1 drug-related death. A phase III clinical trial will be undertaken to further evaluate this regimen (Miller LL, etal, ASCO99, Abs. 1834:475a).

In a phase III clinical trial, a 3-drug combination regimen consisting of cisplatin (50 mg/m^2), gemcitabine (1,000 mg/m^2), and vinorelbine (25 mg/m^2), administered concurrently on day 1 and 8, every 3 weeks, that had been tested in previous phase I (Frasci G, etal, Ann Oncol, Mar 1997, 8(3):291-3) and phase II clinical trials (Comella P, etal, JCO, May 1999, 17(5):1526-34) in chemotherapy-naive patients with advanced nsclc, was compared to cisplatin plus vinorelbine or cisplatin plus gemcitabine in terms

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terms of survival and QoL. This trial, being conducted by the Southern Italy Cooperative Oncology Group (SICOG) of the National Tumor Institute (Naples, Italy), aims to enroll 120 patients in each arm. An interim analysis involving 180 patients (Stage IIIb=63 and Stage IV=117), randomized between March 1997 and October 1998, showed no unexpected toxicity in the 3 arms. Median survival for the entire population was 45 weeks with 91 deaths occurring at a 13-month median follow-up. Accrual continues to the planned final sample size expected to be completed at the end of 1999 (Comella G, etal, ASCO99, Abs. 1876:486a).

A regimen using paclitaxel, carboplatin and vinorelbine, was evaluated in a multicenter phase II clinical trial conducted by the Minnie Pearl Cancer Research Network. Between June 1997 and April 1998, 89 treatment-naive patients with advanced nsclc (Stage IIIb=32 and Stage IV=58) were treated with IV paclitaxel (200 mg/m^2) delivered over 1 hour on day 1, IV carboplatin (AUC=6.0) also administered on day 1, and IV vinorelbine (22.5 mg/m^2) administered on days 1 and either 8 or 15; the regimen was repeated every 21 days. Patients were reassessed after two courses, and responders continued treatment for a maximum of 8 courses. There were 31/89 (35%) major responses to treatment (PR= 29, CR=2). Median survival was 9 months and actuarial 1-year survival is 48%. Myelosuppression was the major toxicity with Grade 3/4 leukopenia and thrombocytopenia occurring in 73% and 3% of patients, respectively. There were 37 episodes of febrile neutropenia among 32 patients, and 4 (4%) treatment related deaths attributable to infection; there were 2 (2%) additional sudden deaths at home that may have been treatment-related. Grade 3/4 nonhematologic toxicities included fatigue (24%), neuropathy (12%), and nausea and vomiting (10%). Although this three-drug regimen is feasible and effective in advanced nsclc, the addition of vinorelbine substantially increased toxicity. This regimen with the vinorelbine dose reduced to 20 mg/m^2 is currently being evaluated as one arm of an ongoing four-arm randomized phase II trial in patients with advanced nsclc (Grimaldi M, ASCO99, Abs. 1954:507a and Hainsworth JD, Chemotherapy Foundation Symposium XVI, Nov 11-13, 1998, Abs. 76:92-93).

A dose-intensive 4-drug combination regimen, involving ifosfamide, carboplatin, etoposide, and paclitaxel (ICE-T), was evaluated in a phase II clinical trial in 41 patients with advanced nsclc (Stage IIIb=32% and Stage IV=68%), to establish its efficacy. The regimen was based in a phase I study, which demonstrated that, with G-CSF support, full-dose, single-agent paclitaxel by 24-hour infusion can be safely administered with full dose ICE chemotherapy in advanced lung cancer (Lynch TJ, ASCO96, Abs. 1114:375). However, in four drug combinations there is the issue of diminishing returns because of marginal effectiveness coupled with high treatment-related toxicity and costs.

A modified protocol, from that used in phase I, consisted of ifosfamide (2,000 mg/m^2) on days 1-3 (with mesna uroprotection), paclitaxel (225 mg/m^2) by a 3-hr infusion on day 1, carboplatin (AUC=5) on day 2, and etoposide (75 mg/m^2) on days 1-3. G-CSF (5 mg/kg/day) was administered from day 4 until the neutrophil count was 3,000 mm^3. At a median follow-up of 12 months, among 36 evaluable patients, the RR was 17%, including 3% CR, 14% PR; disease stabilized in 61%, and progressed in 22%. Among 27 evaluable patients with adenocarcinoma, RR was 15% (4% CR, 11% PR, 67% SD, 18% PD), while among 9 with other histologies, it was 22% (22% PR, 45% SD, and 33% PD). Median survival of all 41 patients was 11.3 months and 1- and 2-year survival was 39% and 0%, respectively. There were no treatment-related deaths, and relatively few patients experienced severe toxicity with Grade 4 neutropenia only observed in 5%, and Grade 3 gastrointestinal, neuromuscular, or hematologic toxicity in 34%. However, while toxicity was manageable, the effectiveness of this intensive combination chemotherapy measured by RR and survival, was disappointing, leading to the conclusion that dose intensive, multi-agent chemotherapy regimens do not provide a therapeutic advantage over less intensive protocols in advanced nsclc (GM Strauss, etal, ASCO99, Abs. 1855:481a).

Editor's note: *Next issue will cover screening, diagnosis, staging and prognosis of lung cancer, and estimate USA populations by type of cancer (sclc and nsclc), and by stage.*

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