FUTURE ONCOLOGY

TECHNOLOGY, PRODUCTS, MARKETS AND SERVICE OPPORTUNITIES

A NEW MEDICINE PUBLICATION | AUGUST 1997 | VOLUME 3, NUMBER 4

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

HEAD AND NECK CANCER — PART I
EPIDEMIOLOGY, ETIOLOGY AND MOLECULAR MARKERS

ANTI-CANCER DRUG DEVELOPMENT

TAXANES — PART I
STATUS OF TAXANES AND THE OUTLOOK FOR GENERIC VERSIONS OF PACLITAXEL

MEETING COVERAGE

NEW APPROACHES IN THE TREATMENT OF GASTROINTESTINAL CANCERS
FROM THE 33RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY DENVER, CO, MAY 17-20, 1997

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

HEAD AND NECK CANCER — PART I

EPIDEMIOLOGY, ETIOLOGY AND MOLECULAR MARKERS

Head and neck cancer comprises a heterogeneous group of malignancies of the upper aerodigestive tract that account for approximately 3% of all new cancers diagnosed in the USA, but are more common in other parts of the world. These cancers include tumors of the salivary glands, nasal cavity, paranasal sinuses, nasopahrynx, oral cavity, oropharynx and hypopharynx. Laryngeal cancer which is sometimes grouped with the oral cavity and pharyngeal cancer or with lung cancer and other respiratory cancers, is not included in this discussion but will be reported separately in an upcoming issue of FUTURE ONCOLOGY. The vast majority of head and neck cancers are squamous cell in origin and these cancers are the focus of this review. Thus, salivary gland cancers, with their distinct histology and epidemiology, will not be considered.

One salient point to consider in reviewing squamous cell carcinoma of the head and neck (HNSCC) is that, in large measure, it is a preventable malignancy. Although the role of genetics and unavoidable environmental exposure should not be ignored, evidence suggests that many of these malignancies arise as a result of life style choices involving abuse of alcohol and, particularly, tobacco. In fact, in many patients with early stage lesions, loss of life is more commonly attributable to comorbid illnesses from such abuse.

EPIDEMIOLOGY

HNSCC is much more common worldwide than in the USA. Exhibit 1 estimates overall incidence and mortality associated with HNSCC in selected world regions; inclusion of laryngeal cancer, increases overall incidence of head and neck cancer by 50%. Incidence and mortality estimates attributable to HNSCC for selected world regions are presented in Exhibits 2 and 3. These estimates include only cancers of the oral cavity and pharynx.

Analysis of the incidence of head and neck cancer by site (see Exhibit 4) reflects the varying etiologies for these cancers from one geographical region to another. For instance, in Hong Kong, Singapore and the Philippines, the overwhelming majority of head and neck cancers are nasopharyngeal cancers, while in France and India such malignancies are primarily localized to the posterior of the mouth (including tongue, salivary glands, floor and roof, and cheek of mouth, and oropharynx). Oral cancer accounts for up to 40% of all malignancies in parts of India and South East Asia. The high percentage of lip cancer cases in countries such as Australia, Spain, Hungary and Belarus, possibly reflect increased use, duration and/or strength of chewing tobacco, or pipe smoking. Cancerous lesions of the buccal mucosa or gingiva are determined by where "snuff" is placed in the mouth. Differences in cancer sites may also reflect oral hygiene, depth of smoke inhalation and the filter quality of the cigarette, cigar, or pipe, or extent of alcohol use.

International Epidemiology

Incidence of head and neck cancer worldwide is estimated at more that 500,000 newly diagnosed cases every year. In most countries, oral cancer is 2 to 3 times more prevalent in males than females, and occurs more often in blacks than whites. The highest incidence of oral cancer in the world has been reported in parts of France, India, and Southeast Asia (Parkin etal, WHO, Cancer Incidence in Five Continents, VI (120), 1992). Higher incidence of nasopharyngeal cancer in China and Hong Kong has been linked to lifelong consumption of salty fish and preserved and fermented foods (Smans M, etal, Atlas of Cancer Mortality in the European Economic Community, IARC WHO 1992;107:59-61). Mortality associated with head and neck cancer is presented in Exhibit 3.

Recently, increases in incidence of oral and pharyngeal cancers have been observed in younger men in the USA and elsewhere. Researchers believe smokeless tobacco may play a role in this increase, however, increases in young men have also been observed in Scotland and other European countries where smokeless tobacco is seldom used (Macfarlane GJ, etal, BMJ 1992; 305:1121-1123).

An analysis of cancer incidence and survival trends in Scotland, between 1968 and 1992, showed that incidence of cancer of the oral cavity and pharynx is rising. Also, relative five-year survival rates for cancers of the tongue, mouth and pharynx, among those under age 65, fell from 47% to 39%. The largest increases in incidence and mortality were in the more socially deprived areas (Macfarlane GJ, etal, Br J Cancer 1996; 73:805-8).

The most common complication associated with the long term management of HNSCC, is the development of second primary tumors after initial cure. It is estimated that 20% to 30% of HNSCC patients develop a second primary tumor of the oral cavity or pharynx within five years of initial therapy. This second primary HNSCC is usually caused by the same carcinogen exposure as the first tumor, thus emphasizing the need to eliminate risk factors.

USA Epidemiology

It is estimated that in 1997, in the USA, there will be approximately 41,600 new cases of head and neck cancer and 12,670 deaths. This represents approximately 3% of all new cases of cancer and 2.3% of all deaths attributed to cancer (CA Cancer Journal for Clinicians 1997; 47:8).

Between 1987 and 1991, incidence of oral cancer, per 100,000 population, was 15.8 among white men, 6.2 among white women, 23.7 among black men, and 6.5

among black women. Over 90% of cases of oral cancer occur in individuals over 45 years-of-age, and the risk continues to increase with age. Generally, incidence is higher in men, although, as is true for other cancers related to smoking, women are being diagnosed at an increasingly higher rate, such that the male to female ratio has declined over the past decades from 5:1 to approximately 3:1. Unfortunately, it appears that at similar levels of tobacco exposure, women may actually have a higher incidence of HNSCC than men (Spitz MR, etal, Cancer, 1988 Jan 1, 61(1):203-8).

Exhibit 1
Estimated Incidence and Mortality of Oral Cavity, Pharynx and Larynx Cancer in Major World Regions in 1997

Region	Oral Cavity & Pharynx		Larynx		Total	
	(#)	(%)	(#)	(%)	(#)	(%)
Incidence						
Europe*	54,527	8.8	33,292	5.4	87,819	14.1
North America	33,840	5.4	45,482	7.3	79,322	12.8
Triad*	93,848	15.1	81,411	13.1	175,260	28.2
World	418,649	67.4	202,381	32.6	621,030	100.0
Mortality						
Europe*	23,031	9.9	13,317	5.7	36,348	15.6
North America	9,510	4.1	18,077	7.8	27,587	11.9
Triad*	34,912	15.0	32,449	14.0	67,360	29.0
World	151,578	65.2	80,836	34.8	232,415	100.0

** Excludes the former USSR*

The most common sites of oral cancer are the tongue, floor of the mouth, gums and other parts of the mouth, lip, oropharynx, and hypopharynx. Among white males, the most common sites are the gums and floor of the mouth, most likely indicative of chewing tobacco as a common etiology. In black males, the most frequent site or oral cancer is the pharynx, most likely caused by smoke inhalation or alcohol use (Day, etal, JNCI 1993; 85:465-473). Exhibit 5 estimates incidence and mortality of HNSCC in North America by anatomical site.

Currently, in the USA, mortality from oral cancer accounts for 2.8% of all cancer deaths in males and 1.4% in females. For years for which data are available, African-Americans have a higher mortality rate than Caucasians (CA Cancer Journal for Clinicians 1997; 47:21).

Despite improved diagnosis and management, long-term survival rates of all types of HNSCC in the USA have not improved significantly over the past three decades; survival rates in American blacks have actually declined. Over the last three decades, oral cavity and pharynx cancer survival rates have remained at 55% in white Americans and between 31% and 36% in black Americans (see Exhibit 6). However, incidence and mortality of these cancers among men, in general, have begun to decline. Just prior to this observed decline, incidence of lung cancer also declined, suggesting that the reason for this phenomenon may be attributable to decreased prevalence of smoking.

ETIOLOGY AND RISK FACTORS

Smoking and alcohol abuse are documented risk factors for oral cancer. Use of tobacco has been most highly correlated with the risk of developing head and neck cancer, increasing the risk from 5%-25% over that of non-smokers. While alcohol consumption is a moderate independent risk factor, combined use of tobacco and alcohol acts synergistically to increase risk. Smokeless tobacco increases risk of premalignant oropharyngeal lesions. Betel nut consumption is strongly associated with increased incidence in parts of the world where this practice is common. Smokeless tobacco contributes to high rates of gum and buccal cancers and premalignant lesions such as leukoplakia. Risk of lip cancer is increased by smoking, especially pipe smoking. Recent case-control studies found that use of mouthwash with high alcohol content may be associated with an increased risk for oropharyngeal malignant tumors (Winn DM, etal, Cancer Research 1991; 51(11):3044-3047; Spitz MR, Seminars in Oncology 1994; 21(3):281-288).

Other predisposing factors for head and neck cancer include exposure to sunlight (lip), asbestos (larynx), shoe polish, wood, or textiles (nasal cavity), nickel (nasal cavity, maxillary sinus) and poor oral hygiene, or ill-fitting dentures. Iron deficient anemia may produce atrophic oral changes, as seen in patients with Plummer-Vinson syndrome, which may lead to cancer of the hypopharynx. Certain skin diseases, such as syphilis or erosive lichen planus, have been associated with the development of tongue cancer (Mahboubi S, Cancer Epidem Prev, 1982; 583-595). Cancer of the salivary gland is rare and is usually related to radiation exposure. Incidence of lip and uveal cancer worldwide is higher in rural populations and lower socioeconomic groups, most likely because of a higher incidence of outdoor occupations (Stein Internal Medicine, 4th Ed, 1994; Part III, Ch 100).

Genetic viruses, such as human papillomaviruses (HPV) and herpes simplex viruses (HSV), may also contribute to head and neck cancer. HPV has been implicated in HNSCC because its DNA has been isolated from malignant cells (Watts SL, etal, Oral Surg Oral Med Oral

Pathol, 1991 Jun, 71(6):701-7). Also, carcinogenesis attributable to these viruses is thought to be co-dependent on promoters such as alcohol, tobacco, and metabolites of chronic inflammation. However, findings suggest that HPV may also play a role in HNSCC in nonsmokers (Fouret P, etal, Archives of Otolaryngology, Head and Neck Surgery, 1997 May, 123(5):513-6).

Diet, particularly vitamin A deficiency, has been weakly linked to the development of head and neck cancer.

Oral Cancer

Oral cancer, although relatively uncommon in the West, accounts for up to 40% of all malignancies in parts of India and South East Asia. Approximately three-fourths of all oral cancers are thought to be caused by tobacco and alcohol abuse. In the largest population-based study of oral cancer, trends in risk were associated independently with duration and type of tobacco use and amount of alcohol consumption. After adjusting for alcohol intake, relative to nonsmokers, those smoking over 40 cigarettes per day for over 20 years, experience a four-fold risk in men and a ten-fold risk in women. After factoring smoking, moderate drinkers (15-29 drinks per week) had a three-fold risk of oral cancer and heavy drinkers (over 30 drinks per week) had an eight- to nine-fold risk. Furthermore, a synergism of risk factors occurred in individuals who consume alcohol and smoke, increasing the risk of developing head and neck cancer to 16- and up to 35-times that for nonsmokers and

Exhibit 2
Estimated Worldwide Incidence of Head and Neck Cancer (Oral Cavity and Pharynx) in 1997

Country	Male		Female		Total	
	Incidence	Rate*	Incidence	Rate*	Incidence	Rate*
Denmark	221	8.5	140	5.3	36	6.9
France	11,738	41.2	2,141	7.1	13,879	23.7
Germany	6,027	14.6	2,187	5.1	8,21	9.8
Greece	389	7.4	153	2.9	542	5.1
Ireland	197	11.1	82	4.6	279	7.8
Italy	5,801	20.7	944	3.2	6,746	11.7
Luxembourg	53	25.4	11	5.1	64	15.1
Netherlands	574	7.4	142	1.8	716	4.6
Portugal	1,015	21.4	264	5.1	1,279	13.0
Spain	5,035	26.2	621	3.1	5,656	14.4
UK, England & Wales	2,227	7.8	1,419	4.8	3,646	6.2
UK, Scotland	189	7.6	79	3.0	268	5.2
EEC Total	33,465	19.6	8,184	4.6	41,649	12.0
Austria	873	22.3	201	4.9	1,074	13.3
Finland	190	7.6	164	6.3	354	6.9
Iceland	5	3.4	6	4.3	10	3.8
Malta	45	23.7	12	6.3	57	14.9
Norway	166	7.6	106	4.8	271	6.2
Sweden	292	6.6	127	2.8	419	4.7
Switzerland	755	21.1	154	4.2	909	12.5
Non-EEC Total	2,326	13.7	769	4.4	3,095	9.0
Bulgaria	739	17.4	189	4.3	928	10.7
Czech Republic	1,027	20.5	199	3.8	1,226	11.9
Hungary	890	18.8	372	7.1	1,262	12.7
Poland	2,919	15.5	656	3.3	3,575	9.2
Romania	2,147	20.6	438	4.0	2,586	12.1
Slovenia	163	19.0	44	4.0	207	10.6
Eastern Europe excludes former USSR	7,886	17.9	1,898	4.1	9,783	10.8
EUROPE Total	43,677	18.9	10,850	4.5	54,527	11.5
Armenia	92	5.4	30	1.7	122	3.5
Belarus	619	12.6	111	2.0	730	7.0
Estonia	162	24.0	37	4.8	198	13.7
Kazakhstan	1,140	14.0	575	6.6	1,716	10.2
Kyrgyzstan	235	10.6	40	1.7	274	6.0
Latvia	110	9.8	26	2.0	136	5.6
Lithuania	406	23.7	82	4.3	488	13.4
Russia	12,317	17.8	4,052	5.1	16,369	11.1
Tajikistan	179	6.0	86	2.9	266	4.4
Ukraine	5,375	22.9	1,397	5.1	6,772	13.4
Uzbekistan	708	6.0	413	3.4	1,122	4.7
Former USSR Total	21,344	16.7	6,850	4.8	28,194	10.4

— continued on next page

nondrinkers. Further evidence of the predominant etiologic role smoking plays in oral cancer is indicated by the decline in risk following cessation of smoking. Individuals who quit smoking for five years had half the risk of oral cancer of continuing smokers, and those who quit smoking for 10 years demonstrated no increased risk. After 15 years of smoking cessation, males no longer exhibited increased risk whereas the risk for females was 1.5 (Spitz MR, etal, Cancer, 1988 Jan 1, 61(1):203-80). Risk increases with increasing number of cigarettes and duration of smoking and decreases as the interval from the time of quitting increases. Smokers of pipes and cigars showed a greater risk for oral cancer than cigarette smokers (Franceschi S, etal, Cancer Res 1990; 50:6502-7).

In a study of 1,009 patients with oral neoplasia and 923 age-matched controls, conducted between 1981 and 1990, increase in risk of oral cancer associated with increase in exposure of cigarette tar, was significantly higher in women than men. Also, in cases of head and neck cancer among nonsmokers, there was a significantly greater proportion of women than men older than 50 years-of-age. These data suggest that women who smoke may require less tar to be much more susceptible to oral cancer than men, and women over age 50 who do not smoke, may be exposed or more susceptible to other carcinogens than men who do not smoke (Muscat JE, etal, Cancer Res 1996; 56:5192-7).

China	37,162	5.9	22,486	3.8	59,648	4.9
Hong Kong	1,155	35.2	448	14.3	1,603	25.0
India	135,448	27.1	68,300	14.6	203,747	21.1
Israel	275	10.0	106	3.8	381	6.9
Japan	3,942	6.4	1,539	2.4	5,481	4.4
Singapore	520	30.1	277	16.0	798	23.0
Thailand	2,378	8.1	1,003	3.3	3,380	5.7
Asia & Other Total	180,880	14.7	94,158	8.1	275,038	11.5
Argentina	2,324	13.1	518	2.9	2,841	7.9
Australia	2,069	22.5	647	7.0	2,716	14.7
Brazil	5,118	6.3	3,561	4.3	8,679	5.3
Chili	470	6.6	147	2.0	617	4.3
Costa Rica	114	6.4	38	2.2	153	4.3
Cuba	978	17.8	371	6.8	1,349	12.3
New Zealand	162	9.1	72	4.0	234	6.5
Paraguay	137	4.8	22	0.8	159	2.8
Peru	75	0.6	37	0.3	113	0.5
Philippines	5,908	15.6	4,282	11.2	10,190	13.4
Oceania & S. America	17,354	9.8	9,696	5.4	27,050	7.6
Canada	2,200	15.3	890	6.0	3,090	10.6
United States	20,900	16.0	9,850	7.2	30,750	11.5
North America	23,100	15.9	10,740	7.1	33,840	11.4
Triad**	70,719	16.1	23,129	5.0	93,848	10.5
World Total	286,355	15.0	132,294	7.0	418,649	11.0

Source: Parkin DM, etal, Cancer Incidence in Five Continents, Vol.VI. IARC Scientific Publication 120; WHO International Agency for Research on Cancer, Lyon, France, 1992; Chapter 11:871-913; WHO, 1995 World Health Statistics Annual Report

** Incidence Rates per 100,000 Population*

*** Excludes the former USSR*

A study of 359 male VA patients with oral cancer and 2,280 controls were assessed for the effect of tobacco smoke and alcoholic beverages on specific sites of the oral mucosa. Results showed tobacco smoking was more strongly associated with soft-palate lesions than with lesions in more anterior sites, and cancers of the floor of the mouth and tongue had higher odds ratios in alcohol drinkers than cancers of other sites (Boffetta P, etal, Int J Cancer 1992; 52:530-3). The 359 males had a total of 424 cancer lesions with the following sites of origin:

Site of Oral Cancer	Cases (%)
Floor of the mouth	42.6
Tongue	13.9
Anterior tonsillar pillar	13.6
Soft palate	12.3
Lingual aspect of retromolar trigone	3.1
Alveolar ridge	1.4
Buccal mucosa	1.1
Hard palate	0.6
Multiple sites	11.4

Research has shown that chewing of betel quids (containing areca nut, tobacco, slaked lime or other species), and smoking of bidi (a tobacco preparation rolled in betel leaf), contribute to the majority of cases of oral cancer in parts of India and Southeast Asia (Mahboubi S, Cancer Epidem Prev, 1982; 583-595; Jayant D, Cancer Detect Prev 1986; 9:207-213). Chewing betel quid is con-

sidered a leading cause of oral submucous fibrosis (OSF) which affects about 2.5 million people, mostly in the Indian subcontinent. In OSF, within a median 10-year follow-up period, incidence of oral cancer was 7.6% (Cox SC and Walker DM, Australian Dental Journal, 1996 Oct, 41(5):294-9). Use of toombak appears to play a major role in the high incidence of oral SCC and neoplasms of the salivary glands in the Sudan (Idris AM, etal, International J Cancer 1995; 61:155-8).

Nasopharyngeal Cancer

Nasopharyngeal cancer (NPC) is believed to be caused by viral, genetic and environmental factors that may act in concert in its development, through a multistep process. Although in most countries NPC is rare with rates of less than 1 per 100,000 per year, it is estimated that in China, Hong Kong, Taiwan, Singapore, South Korea, Malaysia, Indonesia, Thailand, the Philippines and Vietnam, populations at risk exceed 1.7 billion people. In certain Chinese populations the annual incidence of NPC is 15-30 per 100,000. In these populations it is the most common tumor among men and the second most common among women, and it is estimated that annual incidence could be as high as half a million. There is also evidence of high mortality associated with the disorder among black American men age 60-80 years old.

Epidemiological patterns for NPC do not coincide with patterns of oral cancer prevalence. For instance, cigarette smoking is not a major risk factor. The role of viruses and their association with development of NPC is an area of active research. There is much evidence to support an association between infection with Epstein-Barr Virus (EBV) and NPC and the immune response of patients with NPC to EBV is diagnostic of the tumor. Several studies have demonstrated existence of a high correlation between presence of NPC and antibodies to EBV in a host and undifferentiated NPC frequently contains EB viral DNA. A recent review describes evidence for a strong link of EBV and NPC in areas of particularly high incidence of the undifferentiated endemic form of this disease, such as Asia and Africa (Liebowitz D, Semin Oncol 1994 Jun, 21(3):376-81).

MOLECULAR MARKERS

As more is learned about the molecular biology of HNSCC, hereditary and acquired genetic defects are being increasingly linked to the development of this malignancy. It is thought that development of frank malignancy occurs after repeated exposure to carcinogens in genetically susceptible individuals in a step-wise progression of genetic alterations. Studies at the molecular level provide exciting areas of research in the pathogenesis, diagnosis, prognosis, and potentially treatment and prevention of HNSCC. Exhibit 7 lists various selected markers linked to HNSCC. New findings are reported with increasing frequency but often, although a marker is identified, its function remains obsure.

Oncogenes and Tumor Suppressor Genes

The most common allelic loss in head and neck cancers, occurring in two-thirds of all cases of HNSCC, is that involving the 9p21-22 region (Devita, Principles of Oncology, 5th edition, 1997). This region codes for p16, an important inhibitor of the cyclin D system (Cancer Res 1994;54: 3153). It is thought that this mutation acts early in the cascade that results in transformation of normal mucosa to invasive neoplasia.

Amplification of chromosome 11q13 DNA sequences is also detected in approximately 30% of primary HNSCC and has been correlated with the presence of lymph node metastasis. Genes identified within this amplified region include cyclin D1, hst-1, int-2, and more recently, ems-1. The best studied proto-oncogene in HNSCC is cyclin D1. Amplification of this gene and its corresponding mRNA has been correlated with laryngeal cancer (Cancer Res 1994; 54:4813) and disease recurrence (Michalides R, etal, Cancer Research, 1995 Mar 1, 55(5):975-8).

Potential tumor supressor genes in HNSCC are thought to be located in areas of common chromosomal deletions in head and neck cancers, including 3p, 17p, and 13q, and the long arm of chromosome 18. The focus of current research is to define the roles that genes located in these regions may have in the progression of malignant transformation. However, genetic morphology may not prove to be clinically useful, because there exists considerable genetic variation in the various stages of HNSCC as well as in non-malignant tissues and in those with minimal dysplasia.

The p53 gene, well characterized as being abnormally regulated in many malignancies, has been implicated in HNSCC, both in terms of pathogenesis as well as a prognostic indicator. Mutations in this important gene exist synergistically with tobacco and alcohol consumption and provide indirect evidence of the role of this gene in the pathogenesis of HNSCC.

In a study of HNSCC samples, p53 mutations were identified in 11 (28%) of 39 cases, whereas cyclin D1 amplification was observed in 6 (16%) of 37 samples. All six tumors with cyclin D1 amplification also manifested p53 mutations, while an additional five tumors with p53 mutations did not demonstrate cyclin D1 amplification. Statistically significant positive correlation between these two gene alterations raises the possibility that, in carcinogenesis, p53 mutation precedes cyclin D1 amplification (Mineta H, etal, Oral Oncol, 1997 Jan, 33(1):42-6).

The fact that allelic loss of chromosome arm 3p is a frequent event in upper aerodigestive tract SCC, prompted investigation of the role of a recently identified tumor suppressor gene, Von-Hippel Lindau (VHL), that is located at chromosome band 3p25-26. Investigators found that allelic loss of chromosome arm 3p in SCC involves regions surrounding the VHL locus but does not

Exhibit 3
Estimated Worldwide Mortality of Head and Neck Cancer (Oral Cavity and Pharynx) in 1997

Country	Male		Female		Total	
	Mortality	Rate*	Mortality	Rate*	Mortality	Rate*
Denmark	109	4.2	56	2.1	165	3.1
France	4,074	14.3	750	2.5	4,824	8.2
Germany	3,715	9.0	984	2.3	4,699	5.6
Greece	136	2.6	54	1.0	190	1.8
Ireland	69	3.9	29	1.6	98	2.7
Italy	2,550	9.1	649	2.2	3,199	5.6
Luxembourg	19	8.9	4	1.8	22	5.3
Netherlands	225	2.9	95	1.2	320	2.0
Portugal	355	7.5	92	1.8	448	4.5
Spain	1,691	8.8	280	1.4	1,972	5.0
UK, England & Wales	891	3.1	568	1.9	1,458	2.5
UK, Scotland	129	5.2	53	2.0	182	3.6
EEC Total	13,964	8.2	3,613	2.0	17,577	5.0
Austria	306	7.8	70	1.7	376	4.7
Finland	68	2.7	57	2.2	125	2.4
Iceland	2	1.2	2	1.5	4	1.3
Malta	16	8.3	4	2.2	20	5.2
Norway	98	4.5	42	1.9	140	3.2
Sweden	133	3.0	68	1.5	201	2.2
Switzerland	326	9.1	70	1.9	395	5.5
Non-EEC Total	2,326	13.7	769	4.4	3,095	9.0
Bulgaria	259	6.1	66	1.5	325	3.8
Czech Republic	411	8.2	80	1.5	491	4.8
Hungary	592	12.5	130	2.5	722	7.3
Poland	1,318	7.0	338	1.7	1,656	4.3
Romania	751	7.2	153	1.4	905	4.2
Slovenia	80	9.3	15	1.4	95	4.9
Eastern Europe excludes former USSR	3,411	7.7	782	1.7	4,193	4.6
EUROPE Total	18,322	7.9	4,709	1.9	23,031	4.9
Armenia	32	1.9	11	0.6	43	1.2
Belarus	393	8.0	66	1.2	459	4.4
Estonia	57	8.4	15	1.9	71	4.9
Kazakhstan	399	4.9	201	2.3	600	3.6
Kyrgyzstan	82	3.7	14	0.6	96	2.1
Latvia	91	8.1	14	1.1	105	4.3
Lithuania	142	8.3	29	1.5	171	4.7
Russia	6,159	8.9	1,418	1.8	7,577	5.1
Tajikistan	63	2.1	30	1.0	93	1.5
Ukraine	1,881	8.0	489	1.8	2,370	4.7
Uzbekistan	248	2.1	145	1.2	393	1.6
Former USSR Total	9,547	7.5	2,432	1.7	11,979	4.4

— continued on next page

include the VHL gene which does not appear to be involved in the pathogenesis of SCC (Waber PG, etal, Oncogene, 1996 Jan 18, 12(2):365-9). Using microsatellite markers investigators determined that a putative tumor suppressor gene in HNSCC lies in the 3p25.1 region (Rowley H, etal, Archives of Otolaryngology, Head and Neck Surgery, 1996 May, 122(5):497-501).

Loss of heterozygosity (LOH) of 18q in metastatic and locally recurrent tumors, but not in primary tumors from the same patient, suggests that a tumor suppressor gene in this region may be important in the progression of squamous cell carcinoma (Frank CJ, etal, Cancer Research, 1997 Mar 1, 57(5):824-7).

Growth Factors

Growth factors have also been identified that seem to be important in HNSCC. Although it has not been categorically demonstrated that growth factors exert positive regulatory effects in HNSCC, evidence is accumulating regarding negative or suppressive effects of certain growth factors (Devita, Principles of Oncology, 5th edition, 1997).

One such growth factor that has been studied in many malignancies is transforming growth factor β (TGF-β); mutations in the TGF-β receptor were observed in cell lines from patients with HNSCC (van der Velden LA, etal, Head Neck 1993 Mar-Apr, 15(2):133-46). TGF-β and its receptor are involved with an upregulation of negative inhibitors of the cell cycle. Perturbations of this system

may release malignant cells from their normal regulatory control mechanisms. Transforming growth factor-α (TGF-α), a potent mitogen, is also known to play an important role in various neoplasms including oral SCC.

Epidermal growth factor (EGF) enhances human SCC motility and matrix degradation but not growth. Exposure of SCC to EGF, in a dose-dependent manner, led to an increased production of urokinase-type plasminogen activator and M(r) 92 kD matrix metalloproteinase by the cells, suggesting that EGF may promote human SCC invasion and metastasis (Shibata T, etal, Tumour Biology, 1996, 17(3):168-75).

China	13,007	2.1	7,870	1.3	20,877	1.7
Hong Kong	486	14.8	157	5.0	642	10.0
India	47,407	9.5	23,905	5.1	71,312	7.4
Israel	50	1.8	25	0.9	75	1.3
Japan	1,602	2.6	769	1.2	2,371	1.9
Singapore	223	12.9	97	5.6	320	9.2
Thailand	499	1.7	211	0.7	710	1.2
Asia & Other Total	63,272	5.2	33,034	2.8	96,306	4.0
Argentina	813	4.6	181	1.0	994	2.8
Australia	506	5.5	185	2.0	691	3.7
Brazil	1,791	2.2	1,246	1.5	3,038	1.8
Chili	165	2.3	51	0.7	216	1.5
Costa Rica	40	2.2	13	0.8	53	1.5
Cuba	391	7.1	148	2.7	539	4.9
New Zealand	73	4.1	38	2.1	111	3.1
Paraguay	48	1.7	8	0.3	56	1.0
Peru	26	0.2	13	0.1	39	0.2
Philippines	3,295	8.7	1,721	4.5	5,015	6.6
Oceania & S. America	7,148	4.0	3,605	2.0	10,753	3.0
Canada	770	5.4	300	2.0	1,070	3.7
United States	5,600	4.3	2,840	2.1	8,440	3.1
North America	6,370	4.4	3,140	2.1	9,510	3.2
Triad**	26,293	6.0	8,618	1.9	34,912	3.9
World Total	104,659	5.5	46,920	2.5	151,578	4.0

Source: Parkin DM, etal, Cancer Incidence in Five Continents, Vol.VI. IARC Scientific Publication 120; WHO International Agency for Research on Cancer, Lyon, France, 1992; Chapter 11:871-913; WHO, 1995 World Health Statistics Annual Report

**Mortality Rates per 100,000 Population*

*** Excludes the former USSR*

Matrix Metalloproteinases

In order to spread, tumor cells degrade extracellular matrix components (ECM) to invade surrounding tissues. To this effect, cancer cells produce various ECM-degrading enzymes such as matrix metalloproteinases (MMPs), serine proteinases and cathepsins. Co-expression of several members of the MMP family of proteolytic enzymes is a characteristic of human carcinomas. In 21 HNSCC specimens, among the various MMPs, expression of collagenase (MMP-1) and gelatinase 92 kD (MMP-9) varied, but gelatinase 72 kD (MMP-2) and tissue inhibitor of metalloproteinase-1 (TIMP-1) were expressed in nearly all tumors. Tumor-associated MMP expression was strongest in stromal cells near advancing margins but no differences in expression levels were detected between primary and metastatic sites (Charous SJ, etal, Annals of Otology, Rhinology and Laryngology, 1997 Apr, 106(4):271-8).

MMP-2 is believed to be crucial in tumor invasion and metastasis and was shown to be widely expressed in various tissues and to be overexpressed in lung and gastric carcinomas. For example, activation of MMP-2 was observed in all ten HNSCC tissue samples examined. Membrane-type matrix metalloproteinase (MT-MMP) gene is expressed in stromal cells of human colon, breast, and head and neck carcinomas. It is hypothesized that MT-MMP and gelatinase A are cooperating during tumor progression, strengthening the concept that proteolytic activities originating from the stromal component of human carcinomas have a critical role in tumor progression (Okada A, etal, PNAS USA, 1995 Mar 28, 92(7):2730-4).

Among the three types of MT-MMPs, identified as activators of MMP-2, increased expression of the MT1-MMP mRNA transcript was also detected in all eight tissue samples. MT1-MMP positive cells were detected in the majority of these carcinoma tissues (24 of 27). MT1-MMP expression was more intense in moderately and well differentiated tumors than in poorly differentiated ones (Yoshizaki T, etal, Cancer, 1997 Jan 1, 79(1):139-44).

Matrix metalloproteinase-3 (MMP-3) was detected in 37 (56.9%) surgical specimens from 65 patients with oral SCC and there was a positive correlation between the expression of EGFr and MMP-3. Over expression of MMP-3 was associated with an advanced pathological stage, a diffuse invasive mode, and a high incidence of neck

Exhibit 4
Estimated Incidence of Head and Neck Cancer (Oral and Pharynx) and Distribution by Site

Country	Incidence*	Lip (%)	Tongue (%)	Salivary Gland (%)	Mouth (%)	Oropharynx (%)	Nasopharynx (%)
Hong Kong	49.5	0.4	7.7	2.4	6.5	2.8	80.2
France	44.6	7.4	24.9	3.6	32.5	29.1	2.5
India	43.7	2.5	37.8	2.7	37.8	16.7	2.5
Singapore	39.1		12.8	3.3	15.9	2.8	65.2
Australia	29.5	54.2	11.5	5.4	16.3	8.5	4.1
Spain	29.3	41.3	17.7	4.1	18.4	13.3	5.1
Philippines	26.8		15.3	7.1	28.7	5.2	43.7
Thailand	26.3	14.4	17.1	1.9	28.1	12.9	25.5
Switzerland	25.3	12.6	24.1	8.3	26.1	26.1	2.8
Italy	23.9	28.0	15.5	10.0	20.9	21.3	4.2
Hungary	21.5	45.6	26.5		10.2	13.0	4.7
Slovenia	21.2	13.7	21.2	0.9	27.8	32.5	3.8
Slovakia	21.0	28.6	20.0	5.7	22.4	19.0	4.3
Poland	18.8	42.6	15.4	6.4	14.9	14.9	5.9
Germany	17.2	11.0	27.9	7.0	32.0	16.9	5.2
USA	16.5	15.2	23.6	10.3	32.1	14.5	4.2
Canada	16.4	28.7	18.3	8.5	25.6	12.2	6.7
Bermuda	16.3		100.0				
Brazil	14.8		35.1		35.1	29.7	
Belarus	14.6	52.1	13.0	5.5	19.9	5.5	4.1
Cuba	14.6	20.5	24.0	8.2	25.3	15.1	6.8
Russia	14.1	14.9	24.1	11.3	31.2	7.1	11.3
Israel	13.8	49.3	11.6	8.0	12.3	2.2	16.7
New Zealand	13.1	36.6	16.8	12.2	18.3	9.9	6.1
Romania	13.0	55.4	7.7		8.5	10.8	17.7
Kyrgyzstan	12.3	44.7	13.0	12.2	19.5	4.9	5.7
Estonia	11.8	23.7	11.9	8.5	28.0	21.2	6.8
Latvia	11.8	42.4	11.0	7.6	19.5	9.3	10.2
Czech Republic	11.6	24.1	19.0	12.1	19.8	18.1	6.9
Denmark	11.5	26.1	13.0	9.6	27.8	14.8	8.7
UK, Scotland	10.6	18.9	20.8	14.2	32.1	8.5	5.7
Norway	10.3	31.1	19.4	7.8	25.2	10.7	5.8
Finland	9.9	49.5	15.2	12.1	14.1	5.1	4.0
Portugal	9.8	43.9			27.6	28.6	
China	9.7	2.1	3.1	8.2	15.5	10.3	60.8
Sweden	9.4	26.6	16.0	14.9	24.5	10.6	7.4
Algeria	9.1	18.7					81.3
Netherlands	9.0	17.8	23.3	8.9	28.9	16.7	4.4
Japan	8.8	2.3	38.6	12.5	28.4	8.0	10.2
Costa Rica	8.6	19.8	22.1	9.3	20.9	12.8	15.1
Kuwait	7.6	21.1	10.5	17.1	15.8		35.5
England & Wales	6.4	9.4	23.4	14.1	31.3	12.5	9.4
Ireland	6.2	43.5	22.6	11.3	22.6		
Paraguay	5.6		35.7		44.6	19.6	
Iceland	5.3	64.2			35.8		

**Overall incidence of HNSCC for both males and females per 100,000 population*

metastasis (Kusukawa J, etal, Eur J Cancer, Part B, Oral Oncology, 1996 Jul, 32B(4):217-21).

Expression of the recently cloned collagenase-3 (MMP-13) in basal cell carcinomas, is associated with terminal differentiation of epithelial cells. The (MMP-13) gene is activated during skin carcinogenesis, and may play a role in degradation of the ECM associated with malignant epithelial growth (Airola K, Journal of Investigative Dermatology, 1997 Aug, 109 (2):225-31).

Other Molecular Factors

Proliferating cell nuclear antigen (PCNA), a 36 kD nuclear protein, has also been implicated in head and neck cancer as it is overexpressed by four to ten times more in squamous cell tumors than in normal epithelium (Shin DM, etal, JNCI, 16 Jun 1993; 85:971-78). As this protein is involved in the DNA synthesis portion of the cell cycle, it represents an attractive candidate as a possible mechanism of abnormal cell growth.

Finally, mutagen-induced chromosomal fragility has been shown to correlate to an increased risk of developing both primary, and subsequently, secondary HNSCC (Cancer Res 1989- 49-4626).

MOLECULAR EPIDEMIOLOGY

Patterns of gene mutations may be linked to their etiology and, thus, provide a means of identifying environmental factors in cancer risk. However, molecular epidemiology is an inexact science, producing inexplicable and/or conflicting findings. Much of this problem may be attributable to racial and

Exhibit 5
Estimated Number and Percent of New Cases and Deaths by Specific Head and Neck Cancer Sites in North America (1997)

		United States*				Canada**			
Cancer Site	ICD-9	Incidence		Mortality		Incidence		Mortality	
		(#)	(%)	(#)	(%)	(#)	(%)	(#)	(%)
Tongue	141	6,400	15.4	1,820	14.4	541	12.5	230	15.1
Mouth	140,142,144	11,000	26.4	2,500	19.7	1,123	25.9	149	9.8
Pharynx	146,147,148	8,800	21.1	2,030	16.0	789	18.2	259	17.0
Other oral cavity	143,145,149	4,550	10.9	2,090	16.5	597	13.8	350	23.0
Larynx	161	10,900	26.2	4,230	33.4	1,290	29.7	530	34.8
Total	140-149, 161	30,750	100.0	8,440	100.0	3,050	100.0	995	100.0

**Cancer Statistics 1997, Journal of the American Cancer Society; 47(1):8-9.*
***Canadian Cancer Statistics 1997 (estimated from 1992 incidence and 1994 mortality:64-65)*

Exhibit 6
Relative Five Year Survival Rate of Head & Neck Cancer by Race in the USA

Year of Diagnosis	White	Black	Total
1960-1963	45.0	-	-
1970-1973	43.0	-	-
1974-1976	54.9	36.3	53.2
1977-1979	54.2	36.3	52.4
1980-1982	55.1	30.5	52.4
1983-1990	54.6	33.6	52.3

Source: SEER Cancer Statistics Review, 1973-1992.

ethnic variations of affected populations and type and stage of lesions, but other factors, such as non-standard detection and measurement methodologies may play a role.

Variations in the detection of p53 mutations in HNSCC is a case in point. For example, distribution of wild type and mutated p53 differs between tumor types, suggesting environmental exposure as a causative factor. p53 mutation in HNSCC is also considered an early event and, while mutation and LOH at p53 locus are important in the genesis of HNSCC, other mechanisms such as binding of viral and cellular proteins to p53, are also likely to play a role (Pavelic ZP and Gluckman JL, Acta Oto-Laryngologica, Supplement, 1997, 527:21-4). However p53 may not be a universal marker. For instance, it was recently reported that although p53 mutations are common (47%) in tumors obtained from populations of such Western countries as the UK, USA and Australia, they are infrequent (7%) in such Eastern regions as India and SE Asia. Tumors from these latter regions are characterized by involvement of ras oncogenes, including mutation, LOH (H-ras) and amplification (K- and N-ras), events uncommon in the West (Paterson IC, etal, Eur J Cancer, Part B, Oral Oncology, 1996 May, 32B(3):150-3). This result is difficult to interpret in light of other findings that link p53 mutations with smoking and alcohol abuse in the development of HNSCC. For example, use of both alcohol and tobacco almost doubled the rate of p53 mutations in HNSCC compared to smoking alone (Brennan JA, etal, NEJM 1995 Mar 16, 332(11):712-7).

ANTI-CANCER DRUG DEVELOPMENT

TAXANES — PART I

STATUS OF TAXANES AND THE OUTLOOK FOR GENERIC VERSIONS OF PACLITAXEL

Taxanes, mostly paclitaxel (Taxol; Bristol-Myers Squibb), have become the most successful oncology drugs of the 1990s (for a detailed discussion see FO, V1 #7/8) with Taxol evolving into a truly blockbuster drug, a rare status for such an agent in the past, ushering an era of high-priced chemotherapy regimens. The combined worldwide market for Taxol and docetaxel (Taxotere; Rhône-Poulenc Rorer) reached $902 million in 1996. Taxol alone is expected to fetch worldwide revenues of $950 million in 1997 and $1.1 billion in 1998, and global sales of Taxotere are expected to grow from $89 million in 1996 to an estimated $200 million in 1997 and $360 million in 1998. Beyond 1998, Taxol sales may be adversely impacted by competition from lower-priced generics while expanded indications for Taxotere may accelerate its market.

CLINICAL ISSUES

Approved clinical indications for taxanes and those under evaluation have been described in various issues of FUTURE ONCOLOGY. Docetaxel and paclitaxel, the two taxanes currently in clinical use, have been proven effective, as first- or second-line regimens, in the treatment of a variety of late-stage cancers as monotherapy, in combination with various others chemotherapeutic agents and hematopoietic support, and in multimodality regimens involving both drug and radiation therapy; combinations with platinum-based agents are particularly effective.

Taxol

Taxol has been approved in numerous world markets as second-line treatment of advanced ovarian (see FO, pp 551-554) and breast cancer (see FO, pp 436-437). It is believed that paclitaxel is also being used extensively off-label and, in advanced ovarian cancer, first-line therapy using paclitaxel, in combination with cisplatin or carboplatin, has become standard treatment. In October 1996, Taxol was approved in the UK as first-line treatment of advanced ovarian cancer. Taxol is available in most major world markets except Japan.

In August 1997 the FDA approved Taxol's supplementary NDA for treatment of AIDS-related Kaposi's sarcoma (KS), six weeks after it was recommended for approval by the Oncologic Drugs Advisory Committee (ODAC) in June 1997. Taxol has also been designated as an orphan drug for the KS indication. BMS intends to submit an NDA for Taxol as a first-line therapy, in combination with cisplatin, for nsclc by the end of 1997.

Taxotere

Taxotere has been approved as second-line treatment of advanced breast and non small cell lung cancer (nsclc) in various world markets. As of mid-1997, Taxotere had been approved in 51 countries; in 24 of these it is the only agent of its kind to be approved for treatment of patients with advanced nsclc. The approved dosage regimen in nsclc is 60 mg/m^2, administered as a one-hour IV infusion, every three weeks. Side effects of Taxotere include neutropenia, thrombocytopenia, anemia, hypersensitivity, fluid retention, nausea and diarrhea.

Taxotere was launched in Japan in June 1997 for the treatment of nsclc and breast cancer, becoming the first taxane to be approved and marketed in Japan. In the USA, Taxotere is only approved for treatment of locally advanced or metastatic anthracycline-resistant breast cancer. In advanced breast cancer, results with Taxotere have been particularly positive. During the 1997 annual meeting of the American Society of Clinical Oncology, it was reported that phase III clinical trials demonstrated that Taxotere was more effective than doxorubicin in treating metastatic breast cancer. Patients treated with Taxotere experienced a 50% better overall response rate when compared with that of doxorubicin (47.2% for Taxotere versus 31.5% for doxorubicin). Rhône-Poulenc Rorer is conducting additional clinical trials in many other types of cancer.

Paxene

Paxene, a paclitaxel, is in development by Baker Norton Pharmaceuticals (Miami, FL), a unit of Ivax (Miami, FL), in collaboration with NaPro BioTherapeutics (Boulder, Colorado). To avoid problems that may arise in establishing equivalence of the generic version of paclitaxel, Ivax chose to undertake extensive clinical studies in Kaposi's sarcoma (KS) and in several other indications to obtain NDA instead of ANDA approval. To avoid patent issues, the drug is administered via a different schedule than Taxol. NaPro has entered into a 20-year agreement for its bulk paclitaxel with Ivax, granting it rights in North America, Europe, Japan and the rest of the world not covered by the agreement with Faulding, and non-exclusive rights in the former Soviet Union, China, certain countries in the Middle East and the Vatican. In exchange, Ivax has agreed to pay NaPro on a cost plus basis and, in addition, pay NaPro a substantial share of profits. (Simultaneously upon entering into the agreement, Ivax purchased approximately 19.8% of NaPro's then outstanding common stock; as of 12/31/96 it owns 9.4%). Ivax is currently conducting phase III clinical trials with paclitaxel in ovarian, breast and lung cancer. In April 1997, Ivax and NaPro submitted an NDA seeking approval to market Paxene in the USA, for the treatment of KS and, on September 19, 1997, FDA's ODAC recommended approval of Paxene as second-line treatment of refractory KS.

TAXOL PATENT AND EXCLUSIVITY ISSUES

Taxol has become a very important revenue source for BMS and the company is fighting by all means at its disposal to protect its worldwide franchise. Had the company been able to obtain a composition of matter patent when it started developing paclitaxel, it would have enjoyed protection from generic versions until at least 2005. Instead, BMS' exclusivity for Taxol, originally established from its NCI CRADA, is due to expire in the USA in late December 1997. Its exclusivity in Europe, however, does not expire until 2003.

Most observers believe that introduction of a true generic version of Taxol is unlikely in the next few years because of several steps taken by BMS designed to block its potential competitors on many fronts. In the next few years, BMS will likely spend more time and energy in court defending its Taxol exclusivity than in the clinic. In its fight to maintain exclusivity, BMS is relying on a broad strategy (see Exhibit 8), including obtaining Taxol use patents, orphan drug designations for certain indications, and extension of its NCI CRADA covering Taxol which now expires in December 1997. This extension, which requires legislative action, may require too many concessions from BMS, including price reductions, drug access to indigent patients, direct profit sharing and more favorable royalty payments to NCI that holds the license to Taxol and has licensed it exclusively to BMS. The high price, set by BMS in accord with the NCI, supposedly reflected the short exclusivity period of Taxol. It is, therefore, argued that any attempt to extend exclusivity via Waxman/Hatch must involve significant concessions on price.

There are two ways for competitors to enter this market, either by filing an ANDA that claims bioequivalence and, therefore, most likely to come up against Taxol formulation and infusion patents, or by filing NDAs based on clinical trials that rely on different formulation and treatment

ment regimens. This latter strategy, adopted by Ivax, may bypass the Taxol use patents, but it will, undoubtedly, prove costly and time consuming for many of the current developers of alternate paclitaxel preparations and keep them off the market for years to come.

APPROVED/MARKETED GENERIC VERSIONS OF PACLITAXEL

Numerous generic versions of paclitaxel are in development with several already marketed outside the USA. However, no generic version has been approved in the USA. Ironically, the many potential manufacturers of generic versions that have emerged because of the ready availability of non-patentable raw material and the ease of producing bioequivalent versions, may be prevented from selling their versions of paclitaxel because they would be like Taxol in terms of formulation and delivery and, therefore, violate its patents.

Suppliers of Paclitaxel to Drug Companies

Hauser (Boulder, CO) that began manufacturing paclitaxel in 1989, entered into a supply contract with BMS in 1991 which subsequently expired in March 1995. Because Hauser was the original supplier of paclitaxel for BMS, its product is grandfathered regarding its taxane derivative constituents and may not be affected by certain BMS patents. Hauser's process of producing semi-synthetic paclitaxel without using 10-DAB routes was approved by the FDA in October 1994. In May 1994, Hauser entered into an agreement with

Exhibit 7
Molecular Markers Associated with Head and Neck Cancer

Molecular Marker	Description and Possible Role
p16 (MTS-1 or CDKN-2); also see FO, p 594	p16 is contained in a region of chromosome 9p21 that is deleted in 2/3 of cases of HNSCC. Among 46 primary head and neck tumors, 65.2% lacked p16 protein (El-Naggar AK, etal, AACR97, Abs. 2210:330). However, p16 point mutations are rare in HNSCC (Cairns P, etal, Science 1994, 265:415-17).
Cyclin D1, located on chromosome 11q13; also see FO, pp 591-592	Cyclin D1 gene dysregulation enhances genomic instability *in vivo* and subsequent gene amplification in early head and neck cancer; however, although amplification of cyclin D1 appears in some pre-invasive tumors, it is primarily encountered in carcinoma *in situ* and invasive malignancy.
Ems-1, located on chromosome 11q13, encodes cortactin, an 80/85 kD cytoskeletal-associated protein which binds F-actin and is a pp60src substrate	Amplification of ems-1 DNA was detected in 8/16 (50%) HNSCC cell lines and was related directly to overexpression of both forms of cortactin, p80 and p85, at equal intensity. In normal bronchial epithelial cells and tumor cell cultures with single copy ems-1 DNA, low levels of cortactin localized to the cytoplasm and surface membrane in normal cells. In contrast, tumor cells with ems-1 DNA amplification, demonstrated intense, homogeneous cortactin cytoplasmic staining. Overexpression of p80/85 may be useful in identifying 11q13 amplification (Patel AM, etal, Oncogene, 1996 Jan 4, 12(1):31-5).
Cdc25a and cdc25b phosphatases	Cdc25a and cdc25b are transcriptional targets of c-myc; cdc25a, in particular, plays an important role as a mediator of myc functions. These proto-oncogenes are overexpressed in a large fraction of HNSCC (Gasparotto D, etal, Cancer Research, 1997 Jun 15, 57(12):2366-8).
Rb located on chromosome 13q; also see FO, pp 592-593	Loss of 13q was detected in more than 50% of all head and neck tumors and was correlated with invasion. However, of 176 HNSCC, only 8% lacked Rb protein expression (Andl T, etal, AACR97, Abs. 2211:330).
Retinoid acid receptor β (RARβ) located on chromosome 3p24	Deletion of chromosome 3p is common in head and neck tumors and RARβ expression is reduced. RT-PCR ELISA revealed that, in laryngeal tumors, RARβ/β2 microglobulin ratios were 450 (ranging from 115 to 1310), compared to 926 (ranging from 349 to 2155) in normal controls (Castillo L, etal, AACR97, Abs. 173:26).
p53	Approximately 50% of HNSCCs incorporate p53 mutations; however, the role of p53 in the prognosis of HNSCC is inconclusive. In early glottic cancer, overexpression of mutant p53 expression was an independent prognostic factor of recurrence; 82% of relapsed tumors overexpressed mutant p53 compared to 29% of controls (Narayana A, etal, ASCO97, Abs. 1391:390a).
Vascular endothelial growth factor (VEGF)	VEGF appears to be overexpressed in invasive HNSCC and in corresponding lymph node metastases (Sauter E, etal, AACR97, Abs. 2217:331).
Transforming growth factor-β (TGF-β) type II receptor (Tβr-II)	Alterations in nucleic acid sequence and mRNA expression of Tβr-II are prevalent in the development of HNSCC (Wang D, etal, AACR97, Abs. 3800:??). Decreased expression of TGF-beta receptors may play asignificant role in the pathogenesis of HNSCC by allowing uncontrolled cell proliferation (Eisma RJ, etal, Am J Surgery, 1996 Dec, 172(6):641-5).
Transforming growth factor α (TGF-α)	Overproduction of TGF-α by HNSCC correlates with adverse prognosis; downregulation of TGF-α decreases cell proliferation of HNSCC *in vitro.*
Epidermal growth factor (EGF) receptor (EGFr)	Overproduction of EGFr, the cell surface receptor for TGF-α, by head and neck tumors correlates with adverse prognosis; downregulation of EGFr decreases cell proliferation of head and neck squamous carcinoma cells *in vitro*. Among the 65 tumors, 20(30.8%) tested positively for EGFr.

— continued on next page

American Home Products to jointly commercialize paclitaxel and to develop taxane analogs. The agreement guaranteed a minimum payment of $8 million to Hauser over the first three years of the contract, with the two companies sharing development expenses. Under the agreement Hauser is to supply bulk paclitaxel to Wyeth-Ayerst and Immunex (Seattle, WA) for international and domestic markets, respectively. In 1996, Wyeth-Ayerst converted its supply arrangement with Hauser to a nonexclusive basis, permitting Hauser to supply other parties in territories outside NA.

Indena (Milan, Italy), is the main supplier of the Taxol intermediate 10-deacetyl baccatin III to BMS which it harvests from its yew tree cultivations in northeast and Central Italy. In January 1997, BMS extended its supply agreement, in effect since 1992, to 2000. Indena is a major source of active compounds extracted from plants. The company is also developing technologies to cultivate plant cells *in vitro*.

NaPro BioTherapeutics (Boulder, Colorado) uses a proprietary extraction, isolation and purification (EIP) process to produce paclitaxel from the bark of the Pacific yew tree obtained from private sources. The company has adapted its EIP technology to also extract paclitaxel from renewable parts of various species of yews and has contracted with Pacific Biotechnologies (a subsidiary of Pacific Generation Technologies, a Canadian reforestation company), in 1993, and Zelenka Nursery,

Smad4/DPC4 located on the long arm of chromosome 18	The recently discovered Smad genes encode proteins that transduce signals from the TGF-β family of cytokines. Smad4/DPC4 may also prove to be a tumor suppressor gene. Introduction of wild-type chromosome 18 into HNSCC suppressed tumor formation (Reiss M, etal, Cell Growth and Differentiation, 1997 Apr, 8(4):407-15).
CENP-F proliferating cell nuclear antigen (PCNA)	CENP-F accumulates in the nuclear matrix during S-phase and reaches maximum level in G2 and M phase. CENP-F gene amplification correlates with c-myc gene amplification and tumor progression in head and neck tumors (De la Guardia C and BÖez A, AACR97, Abs. 1860:277).
c-myc	c-myc was amplified in 71% of squamous cell carcinoma of the head and neck (De la Guardia C, etal, AACR97, Abs. 1860:277).
eIF4E proto-oncogene	eIF4E was elevated as in all 26 HNSCC surgical margins in contrast to its low expression in benign lesions (Nathan CA, etal, Oncogene, 1997 Jul 31, 15(5):579-84).
Tenascin-C (TN-C) and one of its integrin receptors, αυβ6	TN-C and αυβ6 were identified in oral SCC specimens but neither are expressed in normal oral mucosa (Ramos DM, etal, International Journal of Cancer, 1997 Jul 17, 72(2):369-76).
MDM2 (murine double minute-2)	MDM2, a new proto-oncogene, may be associated with p53 gene products and may negatively affect transcriptional activating functions of p53 in oral SCC. Overexpression of p53 and MDM2 proteins was detected in 52% and 40% of oral SCC, respectively; p53 gene mutation was observed in 31% of carcinoma cases. Therefore, MDM2 protein may be an alternative mechanism causing p53 protein dysfunction in oral SCC (Matsumura T, etal, 1996 Jul-Aug, 53(4):308-12).
Heat shock protein, HSP70	HSP70, a 70 kD heat shock protein, physically associates with p53 in dysplastic oral lesions and SCC; p53-HSP70 complex formation was seen in 19/52 cases of oral SCCs and 10/53 cases of leucoplakia but in none (0/20) of normal cases. p53-HSP70 complex formation may be one of the mechanisms of stabilisation of p53 protein, resulting in increased levels in potentially malignant and malignant oral lesions and may be implicated in oral carcinogenesis (Kaur J, etal, Eur J Cancer, Part B, Oral Oncology, 1996 Jan, 32B(1):45-9).
Metalloproteinase (MMP)-2, a 72 kD type IV collagenase	MMP-2 plays an important role in tumor invasion and metastasis, so MMP-2 could be a useful biological tumor marker for metastasis and prognosis (Kawata R, etal, Nippon Jibiinkoka Gakkai Kaiho Journal of the Oto-Rhino-laryngological Society of Japan, 1996 Feb, 99(2):299-305).
Collagenase-3 (MMP-13)	MMP-13 mRNAs were detected in 22 of 29 HNSCC cell lines (14 of 15 primary HNSCC and 8 of 14 from recurrent tumors or metastases). Also, MMP-13 mRNAs were detected in 15 of 17 HNSCC tumor samples, mostly expressed by tumor cells at the invading front, but in a subset of HNSCC, MMP-13 mRNAs were also expressed by stromal fibroblasts but were not detected in intact skin or oral mucosa. MMP-13 mRNA levels in HNSCC were enhanced by TGFβ, tumor necrosis factor-α, TGF-α, and keratinocyte growth factor (Johansson N, etal, Am J of Pathology, 1997 Aug, 151(2):499-508).
Telomerase	Telomerase activity was detected in 100% of cell lines of HNSCC, 90% of invasive tumors and 100% of dysplastic and hypersplatic lesions; none of normal tissues had detectable telomerase activity (Mao L, etal, Cancer Research, 1996 Dec 15, 56(24):5600-4). Telomerase activity was detectable in 14 of 16 HNSCC and in 10 of 26 oral leukoplakia tissues and its expression in premalignant lesions was associated with phenotypic progression, indicating the degree of dysplasia (Mutirangura A, etal, Cancer Research, 1996 Aug 1, 56(15):3530-3).

Exhibit 8
Taxol Chronology

Event	Comments	Dates
Clinical Issues and Approvals	As of early 1997, Taxol was approved in over 50 countries with the exception of Japan	
Paclitaxel was discovered by NCI researchers and deemed potentially effective as an anti-cancer agent	Originally investigated in 1967, the drug was shelved only to be rediscovered in 1978 and enter human trials in 1984	Early 1960s to mid-1980s
A CRADA was established between BMS and the NCI to develop Taxol as monotherapy (24-hour infusion) for advanced refractory ovarian cancer	Taxol was extracted from the bark of the Pacific yew tree, alarming environmentalists	1989
Approved as second-line therapy in advanced refractory ovarian cancer	Recommended regimen is 3-hour IV infusion of 135 mg/m^2 or 175 mg/m^2, *q* 3 weeks, approved June 22, 1994); original infusion period was 24 hours	December 1992 in the USA and early 1994 in Europe
Approved as first-line treatment of ovarian cancer in the UK		October 1996
Approved as second-line therapy in advanced refractory breast cancer	Recommended regimen is 3-hour IV infusion of 175 mg/m^2, *q* 3 weeks; a 96-hour infusion has also been clinically evaluated	April 13, 1994 in the USA and 1995 in Europe
Approved as second-line therapy in advanced Kaposi's sarcoma	Recommended regimen is 3-hour IV infusion of 100 mg/m^2 or 135 mg/m^2 *q* 3 weeks	August 4, 1997 in the USA
Product Sources and Alliances		
Paclitaxel was extracted from renewable sources	Paclitaxel was subsequently extracted from 10-deacetyl baccatin III (10 DAB), a precursor found in the needles of various species of yew; Hauser that began manufacturing paclitaxel in 1989, entered into a supply contract with BMS in 1991 which subsequently expired in March 1995	Early 1990s
Semi-synthetic paclitaxel	BMS licenses technology from Florida State University (FSU; Tallahassee, FL) to produce its version of semi-synthetic paclitaxel; BMS obtains the paclitaxel precursor used to synthesize Taxol at its Swords, Ireland plant, under an agreement signed in June 1992 with Indena (Milan, Italy) that extracts it from the needles and twigs of the European species of the yew tree	Approved in October 1994 in Europe and in December 1994 in the USA
Synthetic paclitaxel	After considerable effort paclitaxel was synthesized by chemists KC Nicolaou, PhD, and colleagues at Scripps Research Institute (licensed to Ivax) and Robert Holton, PhD, at FSU; it is unlikely that synthetic paclitaxel, that requires several complex steps to produce, will ever be produced in competition with natural and semi-synthetic versions	1994
Cell culture production process	BMS exercised an option to license Phyton's (was Phyton Catalytic; Ithaca, NY) cell culture process to produce Taxol and related products under a multi-year, multi-million agreement; the two companies have been collaborating in this area since 1991 and in 1993 agreed to scale-up production of paclitaxel. Phyton produces paclitaxel at its German subsidiary in Ahrensburg	May 1995
Patents and Related Issues	The original Taxol patents are held by the NCI and licensed exclusively to BMS; new patented improvements have been also licensed to BMS that is estimated to have paid about $30 million in fees	
Exclusivity	Exclusivity of 5 years in the USA and 10 years in Europe from the time of approval was awarded to BMS for developing a non-patentable drug	Expires on December 1997 in the USA and in 2003 in Europe
Infusion patents to limit hematologic and neurologic toxicity	3-hour infusion of 135 mg/m^2 to 175 mg/m^2 (# 5,641,803) or 24-hour infusion regimen of 135 mg/m^2 (# 5,621,001), as well as other use patents all licensed from the NIH	3-hour patent that provides protection until 2102, was awarded in June 1997 and a 24-hour patent in April 1997, in the USA and Europe

— *continued on next page*

Formulation	Stable formulation patent; Taxol must be properly formulated to maintain its activity	Awarded in the USA and Europe in 1996 and 1997
Derivatives	There may be taxane derivatives in the final drug form that may be cytotoxic that are unique to Taxol	Awarded in the USA and Europe in 1994, 1995 and 1996
CRADA extension/legislative intervention	BMS is seeking to extend its CRADA on the ground that it is investing considerable moneys to expand applications of paclitaxel to the benefit of patients that would not be economically feasible if generics force price reductions	1997
Orphan drug designation	BMS obtained orphan drug designation in the USA for treatment of Kaposi's sarcoma (KS)	Request filed in February 1997, approved in August 1997
Litigation	Infringement suits, complaints and injunctions filed by BMS as well as by its future competitors are becoming increasingly commonplace	
Complaint against Biolyse Pharmacoppée Internationale	BMS files a complaint against Biolyse for allegedly misrepresenting its formulation of paclitaxel as being the same as Taxol; it was subsequently settled	Mid-1995
Injunction against F.H. Faulding	BMS sought an injunction to prevent Faulding from continuing to market Anzatax in Australia. In March 1995, an Australian court denied BMS's request to enjoin Faulding from marketing paclitaxel; in 1994 Faulding also took legal action against BMS when it launched Taxol in Australia, seeking to invalidate its patents	February 1995
Infringement suit against Yew Tree Pharmaceuticals and the Dutch College, the regulatory authority that approved Yew Tree's NDA	According to Yew Tree the court in Hague ruled against BMS on July 24, 1997, allowing the drug to remain on the Dutch market where annual paclitaxel sales are estimated at about $10 million	1996-97
Revocation suit filed against BMS by NaPro Biotherapeutics	NaPro filed a revocation of BMS' infusion patents in Europe	1997
Permanent injunction sought by Immunex to have its ANDA reviewed by the FDA prior to December 27, 1997	Immunex submitted its NDA on December 30, 1996	Filed July 25, 1997

a USA horticulture company, in 1996, to grow cloned ornamental yew bushes on a large scale. In 1997 NaPro began construction of a large scale commercial EIP manufacturing facility in Boulder, CO, with planned capacity to meet the forecast commercial needs of its partners through 1999. NaPro is also developing a semi-synthetic process for manufacturing paclitaxel from other renewable biomass sources; a supplemental NDA for this form of paclitaxel is not expected before 1999.

In mid-1996, Imutec (Scarborough, Ontario, Canada) entered into a collaborative research agreement with NaPro to evaluate the efficacy of a combination of Virulizin and paclitaxel, in the treatment of lung adenocarcinoma. The 12-month study is being conducted by Mark Manning at the School of Pharmacy at the University of Colorado Health Sciences Center (Denver, CO).

Marketers of Generic Paclitaxel

Dabur (Delhi, India) a herbal products company, produces semi-synthetic pharmaceutical-grade final-dose form paclitaxel, using leaves and needles of the Himalayan Himalayan yew tree. Dabur markets paclitaxel in India. InNova, its joint venture with ChiRex (Wellesley, MA), established in April 1996, was dissolved in February 1997, but a supply arrangement remains in effect.

F. H. Faulding (Parkside, SA, Australia) entered into a 20-year agreement with NaPro BioTherapeutics, that granted Faulding exclusive rights to NaPro's paclitaxel in ten countries, including Australia, New Zealand and much of Southeast Asia (Singapore, Hong Kong, South Korea, Indonesia, Thailand and Malaysia, among others). Faulding pays NaPro a substantial share of gross revenue.

In January 1995, Faulding obtained marketing approval for Anzatax, its paclitaxel formulation for the treatment of refractory advanced breast and ovarian cancer, in Australia, New Zealand and eight other countries in southeast Asia and certain Middle East markets. Faulding manufactures and packages Anzatax at its David Bull Labs (Mulgrave, Victoria, Australia) facility using the glass vial system Oncotain. In 1996 Anzatax was launched in China (by Foshan Faulding), Hong Kong and to markets in the Middle East.

Immunex (Seattle, WA) obtained approval from the Health Protection Branch of Canada, in July 1997, to market its generic form of paclitaxel. Immunex had filed an AND for paclitaxel in Canada in 1995. Wyeth-Ayerst will manufacture medicinal paclitaxel for Immunex for sale the USA and Canada. In the USA, Immunex attempted unsuccessfully to file an ANDA with the FDA in December 1996, and in July 1997, filed a lawsuit in federal court seeking a permanent injunction to force the FDA to accept its ANDA before the December 1997 lapse of BMS' exclusivity.

Yew Tree Pharmaceuticals (Haarlem, the Netherlands), a joint venture between Hafslund Nycomed (HN; Oslo, Norway) and OPG/Pharmachemie (Haarlem, the Netherlands), was set up to produce generic paclitaxel under the brand name Yewtaxan. In October 1996, Hauser entered into a three-year supply agreement with Yew Tree Pharmaceutical for bulk paclitaxel (a letter of intent was signed in July 1996), worth $11 million, for the Western and Eastern European markets. Yewtaxan was approved in the Netherlands in 1997 for the treatment of advanced breast and ovarian cancer where it has not been launched to date, possibly because of litigation with BMS but was launched in South Africa. Yew Tree plans to enter its paclitaxel into European clinical trials and seek approval throughout Europe.

Next issue: *New sources and generic forms of paclitaxel, new paclitaxel formulations, taxane analogs and derivatives, and novel spindle poisons.*

MEETING COVERAGE

NEW APPROACHES IN THE TREATMENT OF GASTROINTESTINAL CANCERS

FROM THE 33RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY DENVER, CO, MAY 17-20, 1997

GASTRIC CANCER

Monotherapy

Docetaxel demonstrated activity in patients with advanced gastric cancer, particularly chemotherapy-naive patients. In an open-label, non-randomized clinical trial, 57 patients with confirmed advanced gastric cancer and a life expectancy of at least three months, were treated with a one- to two-hour IV infusion of docetaxel (60 mg/m^2), administered every three to four weeks, for at least four cycles. No pre-medication was administered for hypersensitivity reactions or fluid retention but, in cases of Grade 4 neutropenia or leukopenia, granulocyte-colony stimulating factor (G-CSF) was administered subcutaneously. Among 45 evaluable patients, overall objective response rate was 22.2%, with one CR and nine PR. Disease stabilized in 14 patients and progressed in 21. Median duration of response was six weeks, ranging from 4 to 13 weeks. The objective response rate was highest, 40% (4/10), in chemotherapy-naive patients. Grade 3/4 leukopenia and neutropenia were observed in 52.8% and 81.1% of treated patients, respectively. Except for alopecia, other adverse side events, such as vomiting, diarrhea, anorexia, and fatigue, were transient and reversible without any specific treatment (Taguchi T, etal, ASCO97, Abs. 934:263a).

Paclitaxel may also have a role in the treatment of GI cancer as monotherapy or combination therapy. In a phase II clinical trial, 33 chemotherapy-naive patients with advanced gastric adenocarcinoma, were treated with paclitaxel at a starting dose of 200 mg/m^2, administered every three weeks. In the first 15 patients, treatment was administered as a three-hour infusion and, in the subsequent 18, as a 24-hour infusion. All patients were pre-medicated with antihistamines and the H2 blocker cimetidine. G-CSF was used when needed to combat myelosuppression. Among 13 evaluable patients from the initial 15 treated by a 3-hour infusion, objective response rate was 8% (1/13), with one PR and three minor responses (MR). Among 17 evaluable patients from the 18 treated with the 24-hour infusion schedule, the objective response rate was 23%, with four PR and three MR. Overall response rate, for all evaluable patients, was 17% (5/30). Myelosuppression was more severe with the 24-hour infusion schedule although this schedule appeared to show more activity (Aiani JA, etal, ASCO97, Abs.933:263a).

Combination Therapies

Combination therapy with hydroxyurea (Hydrea; Bristol-Myers Squibb), leucovorin (LV), 5-fluorouracil (5-FU), and cisplatin (Platinol; Bristol-Myers Squibb), has been shown to be particularly active in patients with advanced gastric cancer with acceptable toxicity. In a large, multi-center, phase II clinical trial, 102 consecutive patients with pathologically proven advanced gastric adenocarcinoma, were treated with oral hydroxyurea (1.5 gm to 2 gm) on days 0, 1, and 2; LV (200 mg/m^2) as a 2-hour IV infusion and bolus 5-FU (400 mg/m^2) and IV 5-FU (600 mg/m^2), on days 1 and 2; and IV cisplatin (80 mg/m^2) on day 3, every two cycles. Treatment was repeated every 14 days until progression, with at least six cisplatin administrations.

Among 85 evaluable patients, overall objective response rate was 62.4% (53/85), with five CR (5.9%) and 48 PR (56.5%). A weight increase of more than 5% was observed in 48% of patients while symptoms rapidly regressed or disappeared in 73% of those treated. Median follow-up time was 27 months, with a median duration of response of 11 months, a median progression-free survival time of eight months, and a median overall survival time of 11 months. Most common adverse events were vomiting (13% Grade 3), neutropenia (17% Grade 3; 5%

Grade 4), anemia (7% Grade 3; 1% Grade 4), thrombocytopenia (2% Grade 3; 1% Grade 4), mucositis (3.3% Grade 3), and alopecia (4% Grade 3) (Louvet C, etal, ASCO97, Abs. 935:264a).

Irinotecan (Campto; Rhône-Poulenc Rorer) in combination with cisplatin, is highly active in metastatic gastric cancer, resulting in good response rates and significantly improved survival. In a phase II study designed to establish efficacy and feasibility of this combination in the treatment of metastatic gastric cancer, 44 patients were treated with irinotecan (70 mg/m^2) and cisplatin (80 mg/m^2) on day one, and irinotecan (70 mg/m^2) on day 15, repeated every four weeks, until disease progression or unacceptable toxicities were encountered. If myelosuppression was over Grade 2 or diarrhea continued on day 15, the second dose of irinotecan was postponed and, if these toxicities occurred beyond day 22, the second irinotecan dose was skipped. Overall, 146 courses of treatment were administered, with a median of three courses per patient.

Overall response rate among the 44 patients, all of whom were evaluable, was 48% (21/44) with one CR and 20 PR; in those without prior treatment, the response rate was 59% (17/29). Median time to response was 40 days and median PR duration was 176 days. Median survival time was 272 days for all patients and 322 days for those who were not treated with prior chemotherapy. This compares very favorably to the six to seven months median survival time experienced with standard 5-FU and LV therapy (Boku N, etal, ASCO97, Abs. 936:264a).

HEPATOCELLULAR CARCINOMA

Multimodality Therapy

Liver transplantation combined with neoadjuvant and adjuvant chemotherapy is an effective and well tolerated treatment approach for unresectable hepatocellular carcinoma compared to liver transplantation alone, significantly improving outcome and increasing chance for cure. For patients with unresectable hepatocellular carcinoma, only orthotopic liver transplantation offers a chance for cure, but the majority of patients relapse after transplantation. Because promising results were reported using doxorubicin and transplantation together, a prospective, randomized trial was carried out comparing transplantation alone versus transplantation plus 20 cycles of low-dose doxorubicin (total dose 300 mg/m^2) administered pre-, intra-, and post-operatively every week or every two weeks. At the time of this analysis, 42 patients had been randomized, 20 in the combination therapy group and 22 in the transplantation only group. In the treatment group, there were three CR (15%), eight PR (40%), disease stabilized in eight and progressed in one. Those who responded to chemotherapy experienced a significantly improved two-year-survival rate (70%) as compared to controls (45%). No Grade 3/4 drug-related toxicities were observed (Gnant M, etal, ASCO97, Abs. 939:265a).

Intra-arterial Lipodol-iodine 131

A single post-operative adjuvant treatment of 50 mCi of intra-arterial lipodol-iodine 131 (LP-^{131}I), significantly reduces local recurrence rates and significantly increases disease-free survival in patients undergoing definitive hepatic resection for hepatocellular carcinoma. In a prospective randomized study, 30 consecutive patients with operable hepatocellular carcinoma who had undergone definitive resection and recovered from the operation within six weeks, were randomly assigned to either treatment with a single 50 mCi dose of intra-arterial LP-^{131}I or no further treatment. Treatment was administered during selective hepatic angiography. Endpoints such as local recurrence rates, disease-free survival, and overall survival, were measured from the time of operation.

There were three deaths in the LP-^{131}I-treated group, two from recurrent disease and one from liver failure. In those who underwent surgery alone, there were 10 recurrences within a median duration of 5.9 months post-operatively, and six deaths, all caused by recurrent disease. The two-year disease-free survival rate for the LP-^{131}I group was 70% versus 33% for those in the surgery only group. Median overall survival was 46 and 21 months, respectively. Treatment was well tolerated and no complications were encountered (Leung WT, etal, ASCO97, Abs. 988:279a).

PANCREATIC CANCER

PNU-214565

Superantigen-targeted therapy using PNU-214565 (Pharmacia & Upjohn), a recombinant fusion protein composed of staphylococcal enterotoxin A (SEA) and C242 antibody Fab fragment, may prove to be of value in the treatment of patients with advanced GI malignancies, particularly pancreatic cancer. Antibody-directed, superantigen-induced cytotoxicity with PNU-214565, that expresses the CA242 glycoprotein cell surface antigen via the Fab domain of the C242 MAb, has been shown to have potent *in vitro* and *in vivo* anti-tumor effects in preclinical tests.

In this study, 27 patients with advanced GI malignancies were treated with one cycle of PNU-214565 by four consecutive, daily three-hour infusions at doses of 0.15 ng/kg (n=3), 0.5 ng/kg (n=3), 1.5 ng/kg (n=4), 2.75 ng/kg (n=12), 3.5 ng/kg (n=5); dosages were based on an earlier study showing that doses up to 4.0 ng/kg could be safely administered. One person with pancreatic cancer metastatic to the liver experienced a PR of hepatic metastases with stable pancreatic head abnormalities, as demonstrated by CT scan. Pooled analysis of toxicity data on all patients treated thus far, revealed that patients' pre-existing anti-SEA antibodies protect against toxicity at a given ng/kg dose. By jointly considering weight and the concentration of anti-SEA antibodies in a given patient, it is possible to determine a PNU-214565

dose that will induce systemic cytokine release (a surrogate for immunologic activation by uncomplexed drug) without any dose-limiting toxicity (Weiner LM, etal, ASCO97, Abs. 1560:436a).

COLORECTAL CANCER

Monotherapy

AG-337 (Thymitaq; Agouron Pharmaceuticals), a thymidylate synthase inhibitor, has been shown to be safe, well tolerated, and clinically active against adenocarcinoma of the colon. In a phase II, multi-center clinical trial, 17 chemotherapy-naive patients with histologically confirmed adenocarcinoma of the colon, 15 of whom had undergone prior surgery, were administered Thymitaq (1000 mg/m^2 as salt weight), as a five-day continuous infusion, repeated every three weeks. At study entry, thirteen patients had liver and five lung metastases. The number of treatment courses ranged from two to ten; six patients were administered four or more courses. Overall, one patient achieved a PR and disease stabilized in 12, for a median duration of 11 weeks (range 4 to 18 weeks). Serum CEA decreased ≥50% in three patients. Thymitaq was well tolerated and safe, with the most common toxicities being rash, mucositis, and neutropenia of short duration. The activity noted here warrants further study (Belani CP, etal, ASCO97, Abs. 965:272a).

Raltitrexed (Tomudex; Zeneca), another thymidylate synthase inhibitor, has been shown to have an acceptable safety profile and a similar response rate to 5-FU and LV in advanced colorectal cancer, but time-to-disease progression and overall survival were significantly longer for those treated with 5-FU and LV. In a 459-patient, randomized, multi-center, North American trial, 217 patients with advanced colorectal cancer were assigned to raltitrexed at 3.0 mg/m^2, 32 patients to raltitrexed at 4.0 mg/m^2, and 210 patients to 5-FU plus LV. After three therapy-related deaths, the 4.0 mg/m^2 raltitrexed arm was closed and this analysis excludes data from this arm.

At a minimum follow-up of 12 months, there were no significant differences between the groups regarding response rates (14% in the raltitrexed group versus 15% in the 5-FU+LV group) but time-to-disease progression and overall survival time were significantly longer for the 5-FU+LV group. Median survival time was 12.7 months and 9.7 months for the 5-FU+LV and raltitrexed groups, respectively. The raltitrexed group experienced a lower incidence of Grade 3 and 4 oral mucositis (3% versus 10%), diarrhea (10% versus 13%), and leukopenia (18% versus 41%), but a higher incidence of severe asthenia (18% versus 10%), Grade 3 and 4 nausea and vomiting (13% versus 8%) and liver transaminase elevations (7% versus 1%) (Pazdur R, etal, ASCO97, Abs. 801:228a).

Irinotecan has demonstrated an outstanding antitumor activity and prolonged tumor growth control in patients with highly 5-FU-chemoresistant colorectal cancer. Irinotecan was used to treat 455 patients with documented truly 5-FU-resistant colorectal cancer, in four separate phase II trials. Of these patients, 73 were retrospectively identified as 5-FU-resistant from an earlier trial, and 383 were prospectively selected as 5-FU-resistant for three subsequent trials. These 455 patients, all of whom had documented progressive disease at study entry, were treated with IV irinotecan (350 mg/m^2) delivered as a 30- to 90-minute infusion, every three weeks. Treatment continued to a maximum of nine cycles, or until disease progression, or excessive toxicity.

In the 455 treated patients, the overall response rate was 13%, with a median response duration of 7.5 months. Furthermore, 42% of patients were stabilized for a median time of five months. Response rate to irinotecan in this study compared favorably with the 11% to 14% response rate experienced with prior first-line 5-FU therapy. In addition, overall median survival time in the irinotecan-treated patients with advanced colorectal cancer, reached 9.5 months. Median time to disease progression was four months. In these patients, rapidly progressive at study entry, irinotecan therapy (6 cycles) resulted in a 50% probability to be free from progression of disease at four months. Median survival time of patients with either a CR or PR, was 14.5 months, while disease stabilized for 12.5 months. Pain relief was experienced by 61% of responders versus 34% of those with progressive disease, while 74% of responders had performance status of 0 to 1 and increased or stable weight (Van Cutsem E, etal, ASCO97, Abs. 950:268a).

Capecitabine (Xeloda/Seloda; Hoffmann-La Roche), a novel investigational anti-cancer agent, is showing promise in the treatment of patients with advanced stage colorectal cancer, in terms of higher response rates, improved time to disease progression, and fewer drug-related side effects. In a phase II, randomized, multi-center, international clinical trial, 109 patients with advanced colorectal cancer were randomly assigned to one of three dosing schedules of capecitabine, continuous daily treatment with 1331 mg/m^2 (group A), intermittent daily treatment with 2510 mg/m^2 (group B), or intermittent daily treatment with 1657 mg/m^2 plus LV (60 mg/day), orally (group C). The aim of the study was to evaluate safety and efficacy of each schedule.

Overall, 108 patients were evaluable for response, 39 in group A, 34 in group B, and 35 in group C. Confirmed tumor response was seen in 20.5% of those in group A (2 CR, 6 PR), 24% in group B (1 CR, 7 PR), and 22.8% in group C (2 CR, 6 PR). Median time to disease progression was 18 weeks, 33 weeks, and 24 weeks, respectively. Toxicity was mild to moderate in all but one patient, with the most common side effects being diarrhea, gastrointestinal complaints, and stomatitis. No Grade 3 hematologic toxicities were encountered (Findlay MPN, etal, ASCO97, Abs. 798:227a).

Combination Regimens

According to Thierry André, MD, from Hôpital Tenon (Paris, France), adding oxaliplatin (Eloxatine; Sanofi) to bimonthly two-day regimens of high-dose 5-FU+LV, results in a positive clinical benefit in patients who progress on 5-FU+LV bimonthly regimens alone, confirming previous reports of synergy between oxaliplatin and 5-FU in patients with 5-FU-resistant metastatic colorectal cancer. The bimonthly two-day regimen of high-dose bolus and continuous infusion 5-FU+LV, was shown to have a better therapeutic ratio than the Mayo Clinic regimen, while the bimonthly two-day regimen of high-dose LV and high-dose continuous infusion 5-FU, exhibited similar efficacy. Although the addition of oxaliplatin to the continuous infusion of the 5-FU+LV high-dose regimen achieved a high response rate and improved survival in an earlier study ([Eur] Cancer 1997;33:214-219), in this trial the intensive regimen resulted in dose-limiting neutropenia and paresthesia.

To decrease toxicity and improve the therapeutic index, another study was carried out to evaluate combination of oxaliplatin with the two bimonthly regimens. Patients were treated with oxaliplatin (85 mg/m^2) on day one of the same bimonthly 5-FU+LV schedule on which they had progressed. Schedule A (Folfox 3) consisted of oxaliplatin added to LV (200 mg/m^2) as a two-hour infusion on day one of a two-day LV regimen, along with bolus 5-FU (500 mg/m^2) on days one and two, followed by a continuous infusion of 5-FU (600 mg/m^2) on days one and two. Schedule B (Folfox 4) consisted of oxaliplatin added to LV (500 mg/m^2) as a two-hour infusion on day one of a two-day LV regimen, followed by continuous infusion of 5-FU (1500 mg/m^2) on each of the two days. Overall, 86 patients were entered into the study, 52 on Folfox 3 and 34 on Folfox 4.

Of 71 evaluable patients, the overall response rate was 27%. Among 40 patients on Folfox 3, there were 10 PR, disease stabilized in 11 and progressed in 19 patients, for an objective response rate of 25%. Among 31 patients on Folfox 4, there were 9 PR, and disease stabilized in 11 and progressive also in 11, for an objective response rate of 29%. Both regimens were relatively well tolerated, with the limiting toxicity being peripheral neuropathy. No Grade 4 toxicities were observed (André T, etal, ASCO97, Abs. 958:270a).

5-FU Administration Options

According to Phillipe Rougier, MD, of Institute Gustave Roussy (Villejuif, France), continuous infusion of 5-FU is superior to intravenous bolus administration, in terms of tumor response and survival, although median survival times for the two regimens are similar. In a meta-analysis of six properly randomized clinical trials comparing bolus to continuous infusion of 5-FU for treatment of advanced colorectal cancer, endpoints were tumor response, overall survival, and toxicity. Overall, 1219 patients with advanced colorectal cancer were included in the analysis which was strictly based on intent to treat, without patient exclusion.

Objective tumor responses were observed in 14% of patients treated with bolus 5-FU and 22% with continuous infusion. In multivariate analyses, allocated treatment and performance status were significant predictors of tumor response. Median survival was 11.3 months for those on bolus 5-FU compared with 12.1 months for those treated with the continuous infusion regimen which proved more effective both in terms of response rates and median survival period. Independent significant predictors of survival included regimen, performance status, and primary tumor site; outcome of patients with rectal cancer was more favorable (Rougier P, etal, ASCO97, Abs. 946:267a).

Multimodality Therapy

Chemoradiation is safe, well-tolerated, and effective in sphincter-sparing surgery for low lying rectal cancer. Twenty nine patients with histologically proven adenocarcinoma of the rectum who, according to preoperative assessment, would otherwise require abdominoperineal resection (APR), were treated preoperatively with 5-FU (300 mg/m^2) as a daily continuous infusion, for five days-a-week, for six consecutive weeks. All patients were also treated with concurrent radiotherapy to the pelvic area using a dose of 4500 centiGray (cGy) divided in 25 fractions. An additional radiation boost of 900 cGy in five fractions was administered to the tumor area. Six weeks after completion of pre-operative therapy, these patients underwent APR or sphincter sparing surgery. All patients completed preoperative radiation therapy but three patients discontinued chemotherapy because of Grade 3 or higher toxicity. Twenty two patients underwent sphincter sparing surgery and seven patients APR. Four patients achieved a pathological CR and 10 were left with only microscopic evidence of disease (six in the primary tumor site and four in the lymph nodes). At a median follow-up of 12 months, failure-free survival for all patients was 87% and for those undergoing sphincter sparing surgery, 90%. There was one relapse at the anastomotic site and four patients relapsed at distant sites (Maghfoor I, etal, ASCO97, Abs. 971:274a).

CARCINOID SYNDROME

Octreotide Acetate LAR

Octreotide acetate LAR (Sandostatin LAR; Novartis) is an effective and improved treatment approach for patients with carcinoid syndrome usually caused by metastatic intestinal carcinoid tumors that secrete excessive amounts of vasoactive substances. To determine whether intramuscular octreotide acetate LAR, administered every four weeks, was as effective in controlling symptoms of malignant carcinoid syndrome as the thrice daily subcutaneous version, 93 patients were entered into a phase III clinical trial and randomized to octreotide acetate LAR at 10 mg (n=32), 20 mg (n=20), or

INDEX OF COMPANIES & INSTITUTIONS

— continued from page 623

30 mg (n=25), and octreotide acetate SQ (n=26). Those entering the trial were selected because they had demonstrated control of flushing and/or diarrhea while taking SQ octreotide acetate and became eligible when their symptoms returned during a wash-out period of the drug. Eighty patients were evaluable for efficacy and toxicity.

All doses were well tolerated, the most frequent adverse events being flatulence, nausea and abdominal pain. In the 10 mg group, mean daily wash-out flushes were 3.8 and mean daily bowel movements were 5.8. At week 24 of treatment, these were 0.9 and 3.2, respectively. In the 20 mg group, mean daily wash-out flushes were 7.3 and mean daily bowel movements were 5.2. At week 24 of treatment, they were 1.0 and 2.4, respectively. In the 30 mg group, mean daily wash-out flushes were 9.1 and mean daily bowel movements were 5.6. At week 24 of treatment, they were 0.7 and 2.5, respectively. In the SQ group, mean daily wash-out flushes were 4.1 and mean daily bowel movements were 6.1. At 24 weeks of treatment, they were 0.4 and 2.7, respectively (Rubin J, etal, ASCO97, Abs. 993:280a).

FUTURE ONCOLOGY

PUBLISHED BY **NEW MEDICINE, INC.**

PUBLISHER AND EDITOR:	**Katie Siafaca, MS**
EPIDEMIOLOGY:	**Kristina Lorenson, MPH**
SCIENCE & TECHNOLOGY:	**Diane Etchison, PhD**
CIRCULATION:	**Feisal Yamani**
DATABASE MANAGER:	**Raaj Trivedi**
DATABASE CONSULTANT:	**Richard Glenn Williams**
DESIGN & PRODUCTION:	**Jill Burch**

EDITORIAL BOARD

BIOTECHNOLOGY & APPLIED SCIENCES:
James W. Hawkins, PhD, Editor, Antisense Research and Development

CLINICAL PRACTICE:
Ante Lundberg, MD, Dana-Farber Cancer Institute and Harvard Medical School

REIMBURSEMENT AND MANAGED CARE:
Elan Rubinstein, PharmD, MPH, Consultant

TECHNOLOGY AND DEVICES:
Marvin Burns, MBA, President, Bio-Tech Systems

NEW MEDICINE, INC. MAILING ADDRESS:

P.O. Box 909
Lake Forest, California 92630
Tel: 714. 830. 0448 ■ Fax: 714. 830. 0887
e-mail: newmedinc@aol.com
www:http://www.wp.com/new_med/

SUBSCRIPTION INFORMATION:

- FUTURE ONCOLOGY (ISSN 1082-331X) is published as 10 issues (two double issues) per year, with a free annual index listing companies/institutions and subjects covered.
- A one-year subscription, sent first class to U.S. addresses is US $720. A one-year subscription, sent air mail to addresses outside the U.S., is US $780.
- One-year's subscription, (issues V3 #1 to V3 #12), plus back issues (V1 and V2) is $1,840 (U.S.) and $2,100 (outside the U.S.).
- Additional subscriptions sent in the same envelope are $390 each.
- Back issues (V1 and V2) are $600 and $720, respectively, in the U.S. and $630 and $780, respectively, outside U.S.
- Payment must accompany your order; checks must be drawn on a U.S. bank. (A purchase order number is acceptable; however, the subscription will not begin until payment is received.) Make checks payable to New Medicine. Payment may also be made by AMERICAN EXPRESS, VISA or MASTERCARD and wire transfer; please call 714. 830. 0448.