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VOLUME 1 REVIEW

This issue of FUTURE ONCOLOGY, the last of Volume 1, updates developments in subjects covered in the past year. Whenever possible references to previous articles have been incorporated for continuity.

ONCOLOGY DRUGS MARKET TRENDS

Prices Rise in the USA

According to the U.S. Bureau of Labor Statistics, overall manufacturer's prices of branded prescription pharmaceutical rose 4.2% in December 1995, compared to December 1994. Prices of oncology drugs rose by 3.9%.

Oncology Drug Revenues Grow

Worldwide sales of oncology drugs grew significantly in 1995 with most major manufacturers reporting increased sales. Bristol-Myers Squibb (BMS), the leading supplier of cytostatics, reported a 20% global sales growth in its oncology

product line in 1995, with total sales reaching $1.6 billion, compared to 1.3 billion in 1994. In the USA BMS sales grew 14.6% in 1995, to reach $1,060 million, compared to $925 million in 1994. Zeneca, another major supplier of anticancer drugs, posted a 16% sales growth worldwide, with total oncology sales reaching $964.7 million, aided by a 26% increase in sales of Zoladex. Glaxo Wellcome reported only a 5% sales increase in its oncology-related product line worldwide, but sales outside Europe and the USA grew at 22%. Worldwide sales of Schering-Plough's Eulexin grew at a rate of 26% to reach $290 million. Pharmacia & Upjohn reported oncology-related sales of $566.2 million, up 6.7% from 1994 levels, despite a drop in Adriamycin sales.

REGULATORY DEVELOPMENTS

Several favorable regulatory developments are impacting the oncology market.

Acceleration of Oncology Drug Approvals

Governmental initiatives that would accept tumor shrinkage rather than proof of clinical benefit or survival as an end-point in determining effectiveness of oncology drugs, may speed marketing approvals. However, manufacturers of drugs approved on this accelerated basis would have to conduct post-marketing phase III studies. Drug approval may be withdrawn for failure to carry out such studies or if their results depart from original findings. Two drugs, dexrazoxane (Zinecard; Pharmacia & Upjohn) and liposomal doxorubicin (Doxil; Sequus Pharmaceuticals) were approved under this program in 1995. Zinecard was in FDA review for 9.7 months. Under current initiatives average review times for chemotherapeutics and adjunct therapies may take only six months. Also, approval may some day be based on markers that are linked to tumor response but, to date, such markers have not been definitively associated with outcomes.

The FDA would also allow expanded access to drugs approved abroad, encouraging the filing of INDs either by a USA-based sponsor or by the original developer of the drug.

Generally, the oncology market has expanded significantly in the past 12 months. Novel oncology drugs approved by the FDA in 1995 include anastrozole (Arimidex; Zeneca) for advanced breast cancer, bicalutamide (Casodex; Zeneca) for advanced prostate cancer, amifostine (Ethyol; U.S. Bioscience) for chemoprotection, and porfimer sodium (Photofrin; QLT PhotoTherapeutics) for advanced esophageal cancer. Several oncology therapeutics and *in vivo* diagnostics were also recommended for approval and, barring problems at the FDA, they should be entering the USA market in the next 12-18 months.

Less Restrictive Dissemination of Oncology Product Information

In December 1995, the FDA proposed a relaxation of its policies regarding dissemination of information about products used in oncology. Under the guidelines, distribution of reprints of peer-reviewed journal articles and reference texts covering oncology products would be allowed if the main subject is an approved indication and differences in use from labeling instructions are noted. However, the principal topic of the article must be use or indication approved by the FDA. Manufacturers would like these proposed guidelines further expanded to allow dissemination of articles on uses of drugs in combination and adjunct therapies and on new dosing levels, treatment schedules and routes of administration that depart from label instructions.

The oncology community has urged the FDA to relax its information dissemination policies in the cancer area to allow clinicians access to rapidly evolving data on new uses for approved drugs. Because, traditionally, most manufacturers do not seek approval for other "smaller" indications after their drugs are approved for a key indication, off-label use, based on clinical trial results, has been the mainstay of cancer chemotherapy. The Omnibus Budget Reconciliation Act of 1993 has mandated that Medicare cover off-label use of oncology drugs based on information presented in medical compendia and peer-reviewed literature. The FDA would have preferred literature-based NDA submissions for supplemental indications but the industry balked, citing potential FDA delays. Although off-label use is here to stay for the near-term, the agency would rather opt for a system that would review literature-based NDA supplemental submissions to the satisfaction of drug developers and the oncology community at large.

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

This section describes selected new developments in the management of certain cancers originally covered in various issues of Volume 1 of FUTURE ONCOLOGY. Exhibit 1 lists additional drugs in development or presents amended information on drugs reported in previous issues. Exhibits 2 and 3 update epidemiologic data relevant to newly approved agents.

ESOPHAGEAL CANCER

The approval of QLT PhotoTherapeutics' photodynamic therapy for the palliation of advanced esophageal cancer brought into focus this relatively rare but deadly malignancy. For detailed information on esophageal cancer and its management, please see FO, V1 #1, pp 2-3 and #2/3, pp 34, 40-41 & 57-64.

Epidemiology Update

Incidence and mortality rates of esophageal cancer have been rising in the USA and in most other countries (see Exhibit 2). Exceptionally high incidence rates ranging from 126-150/100,000 have been reported from Central

Exhibit I
Update on Anticancer Drugs in Development

Developer/ Collaborator/ Affiliate	Generic Name/ Number/Brand Name	Drug Type/Mechanism/ Target/Delivery	Status/Location/ Indication	Comments
GI CANCER THERAPEUTICS (see FO, V1 #2/3, pp 34-64)				
Agouron Pharmaceuticals/ Cancer Research Campaign	AG337/Thymitaq	Thymidylate synthase inhibitor/IV, PO, IP	Phase II (c96)/USA/ head & neck, pancreas, colorectal and primary liver cancer and nsclc; phase III (11/95)/USA/ head & neck and primary liver cancer	
Bristol-Myers Squibb	BR96-Dox/BMS-182248	Chimeric MAb conjugated to doxorubicin/IV	Phase II (12/94)/USA/ colorectal cancer	Also phase II in lung cancer
Glaxo Wellcome	5-ethynyluracil (5-EU)/776C85	Chemomodulator/potent dehydrogenase inhibitor (the enzyme that rapidly degrades 5-FU)/IP, SC, IV, PO	Phase I/II (10/95)/USA, UK/advanced colon carcinoma	
Glaxo Wellcome	668W95	Virus-delivered enzyme prodrug therapy	Preclin/USA/hepatic metastasis and colorectal cancer	
Hoffmann-La Roche	Galocitabine/Ro-09-1390	Prodrug of doxifluridine	Phase I (9/84)/USA/ stomach, colon cancer	
Isis/Novartis (Ciba)	ISIS-5132/CGP 69846A	Antisense oligonucleotide/ targets the C-raf mRNA involved in signal transduction	Phase I/USA/solid tumors (colorectal and pancreatic cancer)	Also nsclc and malignant melanoma
Lipha (Merck KGaA)/ Cancer Research Campaign	Mitoflaxone/LM-975, NSC-347512	Flavone-8-acetic acid/ induces cytokine production and natural killer (NK) cell activity/IV	Phase I/II/Germany; phase I/USA/colon carcinoma (in combination with IL-2)	Combination with IL-2 was very toxic and not effective
MethylGene (Hybridon)/ McGill U		Antisense oligonucleotides/inhibit DNA methyltransferase	Research/Canada/ colon cancer	Also breast cancer and sclc
MGI Pharma/ Dainippon (Japan)	Acylfulvenes/MGI 114	Semisynthetic compound; natural product derived from *Omphalotus illudens* mushroom	Phase I (b12/95)/USA/ colon cancer	
Neoprobe	RIGS/ACT	Immunotherapy/harvesting of positive lymph nodes, *ex vivo* activation and multi-plication and reinfusion	Phase I/II/USA/late-stage colorectal cancer	
Pharmacia & Upjohn	Spherex		A95/Japan/liver metastases	
Protein Design Labs/ Novartis (Sandoz)	Smart ABL 364	IgG_1 MAb (humanized) against $Lewis^y$ carbohydrate antigen	Preclin/USA/metastatic colorectal cancer	Also prostate and breast cancer; Sandoz conducted phase II clinical trials with the murine version which has been discontinued
QLT PhotoTherapeutics (was Quadra Logic Technologies)/Ligand (Canada); Sanofi Winthrop (USA); Lederle Japan (American Home Products and Takeda jv; marketing, Japan)	Porfimer sodium; dihematoporphyrin ether/ CL-184116/Photofrin	Photodynamic Therapy	A (12/95)/USA (orphan drug)/refractory esophageal cancer; A(7/95)/Canada/ esophageal cancer; L (4/95)/Japan/esophageal, gastric cancer; reg/ Netherlands,France/ esophageal cancer	

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Sandoz	SDZ 62-434, 53	Platelet activating factor (PAF) receptor antagonist	Phase 1/USA/solid tumors	Houlihan WJ, etal, Journal of Medicinal Chemistry, 1995 Jan 20, 38(2):234-40
Servier/Institut Gustave Roussy	S-9788	MDR-reversing agent/in conjunction with doxorubicin and vinca alkaloids	Phase II/France/colon carcinoma in combination with doxorubicin or adriamycin in patients with refractory cancer	Goncalves E, etal, Proc ASCO, [1995] 14:182, Abs. 411 and Tueni E, etal, Abs. 413
Yakult Honsha/Daiichi Pharmaceutical (Japan); Pharmacia & Upjohn (USA; co-promoted by Daiichi); Rhône-Poulenc Rorer (elsewhere)	Irinotecan/CPT-11; DQ-2805; SN-38/Campto (Europe), Topotecin (Japan), Camptosar (USA)	Semisynthetic analogue of camptothecin/topoisomerase I inhibitor/injectable	L (4/94)/Japan; PLA (1/95)/USA; L (9/95)/France/second-line therapy for colorectal cancer; phase II/Japan/stomach and pancreatic cancer	Phase II/USA/sclc, nsclc; reg (1/95)/Japan/primary lung cancer (also see FO, V1 #1 and #2/3)
Zeneca/CRC Technology	ZD-2767	Antibody-directed enzyme prodrug therapy (ADEPT)/prodrug generates the corresponding active drug upon interaction with a bacterial nitroreductase conjugated to MAbs that recognize tumor-selective antigens	Preclin/UK/solid tumors, lung cancer	In the case of actinomycin D, drug to prodrug dose ratio for similar cytotoxicity was greater than 100; prodrug was less toxic (20-100x) *in vivo* (Mauger AB, etal, J Medicinal Chemistry, 1994 Oct 14, 37(21): 3452-8)
Zeneca/BTG	Raltitrexed/ZD-1694; ICI-D-1694/Tomudex	Thymidylate synthase inhibitor/IV	A(8/95)/UK/first-line therapy for advanced colorectal cancer; phase II/USA/pancreatic cancer	
LUNG CANCER THERAPEUTICS (see FO, V1 #4, pp 82-102)				
Agouron Pharmaceuticals	AG3340	Small molecule/matrix metalloproteinase inhibitor/PO, IP	Preclin/USA	
Glaxo Wellcome	3622W94	MAb	Preclin/USA/lung cancer	Also prostate and gastric cancer
Glaxo Wellcome	1209W95	MAb	Preclin/USA/lung cancer	Also prostate and gastric cancer
Rhône-Poulenc Rorer	p53/retroviral delivery		Phase I (9/95)/USA/nsclc	
Sugen	PDGF RTK antagonist/SU101	Small molecule inhibitors of PDGF receptor	Phase 1/USA	
Sugen	HER-2 antagonists	Small molecule inhibitors of HER-2	Preclin/USA	
Transgène/Institut Gustave Roussy		Gene therapy/delivery of cytokine genes using an adenovirus vector/intratumoral	Phase I (10/95)/France/inoperable lung cancer	Tursz T, ECCO8, Abs. 610
MELANOMA THERAPEUTICS (see FO, V1 #6, pp 142-158)				
Bristol-Myers Squibb	BMS-182248-01; BR96-DOX	Immunoconjugate/chimeric (mouse-human) IgG_1 anti-Lewis^y MAb conjugated to doxorubicin/RNA synthesis inhibitor/targets epithelial cancer	Phase I/USA	

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Genetronics		Electrically-enhanced intratumoral delivery of bleomycin	Phase I/USA/melanoma, basal cell carcinoma, Kaposi's sarcoma	Preclin/USA/ pancreatic cancer
Hemispherex Biopharma (was HEM Pharmaceuticals)	Ampligen		Phase II/Canada/ melanoma (also has IND for renal cell carcinoma)	Phase II/III/ Canada/antiviral in chronic fatigue syndrome and encephalomyelitis; phase II/USA/HBV
Lynx Therapeutics/Regina Elena Cancer Institute (Rome) and The Jefferson Cancer Institute		Antisense oligonucleotide/ targets c-myc oncogene	Preclin/USA/	Loretti C, etal, J NCI, Apr 3, 1996, 88(7):419-429
ProScript/NCI		Small molecules/ proteasome inhibitors/ inhibit degradation of p53 and cyclins/PO	Research/USA	Also lung, breast and colon cancer
Rhône-Poulenc Rorer	Retrovirus HS-TK		Phase I/USA	
Sequana Therapeutics/NCI				Identified mutations in gene CDK4 that increase the risk of hereditary melanoma (1/96)
APOPTOSIS INDUCERS (see FO, V1 #1, pp 22-31)				
Milkhaus Laboratory/ New York Medical College	LDI-200	A formulation of chorionic gonadotropin	Phase I/II/USA/leukemia	IND filed (as of 10/95)/USA/ cancer pain; INDs for ovarian cancer and Kaposi's sarcoma pending
ANGIOGENESIS INHIBITORS (see FO, V1 #7/8, pp 185–199)				
Angiogenesis Technology (Angiotech)	Vanadate, orthovanadate	Vanadium compound/ may involve intracellular generation of hydroxyl or vanadium radicals	Research/Canada	
Bristol-Myers Squibb	Acidic and basic FGF-Pseudomonas exotoxin fusion proteins (aFGF-PE40 and aFGF-PE40 KDEL and bFGF-PE40 and bFGF-PE4E KDEL)	Fusion protein/tumor cells bearing FGF-receptors/ angiogenesis inhibitor	Preclin/USA/colon, and hepatocellular cancer	
EntreMed/Children's Hospital, Boston (developer); Bristol-Myers Squibb (ww licensor)	Thalidomide analog	Blocks TNF-α formation	Phase II/USA/prostate, breast and brain cancer and Kaposi's sarcoma	
EntreMed/Children's Hospital, Boston (developer); Bristol-Myers Squibb (ww licensor)	Angiostatin	Natural protein/ prevents metastasis	Preclin/USA	
Prizm Pharmaceuticals		Small molecule/inhibits FGF-2 export pathway and reduces extracellular availability of bFGF/FGF-2	Research/USA	

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Texas Biotechnology	TBC1635	VEGF antagonist	Research/USA/solid tumors	
Xoma	Bactericidal/permeability-increasing protein (BPI) derivatives	BPI N-terminal fragments and peptides/bind and neutralize anticoagulant activity of heparin	Research/USA	
MDR REVERSING AGENTS (see FO, V1 #5, pp 129-136)				
Innovir/Yale University	EGS technology, APL EGS, CMO EGS, hepatitis-B EGS, MDR EGS	Small RNA segment drugs [external guide sequences (EGS)]/redirect RNase P enzyme molecules from their natural targets to cleave a wide range of disease-causing RNA molecules	Preclin/USA/leukemia, cancer multiple drug resistance gene	
Glaxo Wellcome	GF-120918	Radio and chemosensitizer/P-gp inhibitor	Phase II (10/95)/USA, UK/solid tumors	
Sandoz	PSC-833	A non immunosuppressive, non nephrotoxic analog of cyclosporine A	Phase II/III/USA, Europe/prostate, breast, lung and ovarian cancer and non-Hodgkin's lymphoma	
PLATINUM COMPOUNDS (see FO, V1 #1, pp 16-21)				
Asta Medica	Lobaplatin/D-18621, D-19466	Cis-platinum complex of aminomethyl substituted cyclobutane	Phase II/solid tumors	Side effects include thrombocytopenia, leucopenia, nausea and emesis
Bristol-Myers Squibb	BMS-182751	Platinum compound/oral	Phase II	
Debiopharm/Roger Bellon (Rhône-Poulenc Rorer), Sanofi Winthrop	Oxaliplatin/1670RB; RP 54780/L-OHP, Eloxatin	Trans ammine (cyclohexylamine) dichloro dihydroxo platinum (IV)	Prereg/France/advanced malignant melanoma, non-Hodgkin's lymphoma	
Johnson Matthey/Institute for Cancer Research (UK)/Bristol-Myers Squibb	JM-216 (JM-118; JM-219; JM-225; JM-251; JM-269)	Bis-acetato-ammine dichloro (cyclohexylamine) platinum (IV)/oral	Phase II/USA/ovarian cancer, nsclc and mesothelioma	
DIAGNOSTIC RADIOPHARMACEUTICALS (see FO, V1, #2/3, pp 64-72)				
AltaRex/Resolution Pharmaceuticals (Allelix and Nordion International jv)	OVAREX	^{99m}Tc-labeled anti-idiotypic MAb/binds with high affinity to CA 125	Clinical/Europe/ovarian cancer	In advanced clinical development as a vaccine, also in development in radioimmunotherapy and photodynamic therapy
Antisoma/Royal Postgraduate Medical School, Hammersmith Hospital	AS 109	^{99m}Tc-labeled synthetic pentadecapeptide (alpha M2) derived from the third heavy-chain complementarity-determining region (CDR-3H) of a tumor-associated MAb directed against the pancarcinoma cell-surface antigen, polymorphic epithelial mucin/IV	Phase II (95)/Europe, Greece/primary, recurrent and metastatic breast, stomach, colon and ovarian cancer	Also collaborating with Nihon Medi-Physics on a variant of AS 109 for GI cancer
Cytoclonal Pharmaceutics	LCG MAb	Murine MAb/recognizes LCG protein on cancer cells/linked to a radioisotope	Phase I/USA/nsclc	A humanized version is being developed; other MAbs are in development for melanoma and breast and ovarian cancer

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Cytogen	OncoScint CR/OV	Satumomab pendetide/ B72.3 MAb conjugated to ^{111}I	Phase II (12/95)/USA/ breast cancer	
IDEC Pharmaceuticals	IDEC-In2B8	Anti-CD20 MAb coupled to ^{111}I	Phase I/USA/B cell NHL	Genentech has option
Immunomedics/ Pharmacia, Mallinckrodt Medical BV (marketing, Europe)	Arcitumomab/CEA-Scan (was ImmuRAID-CEA)	^{99m}Tc-labeled Fab' fragment of murine anti-CEA IMMU-4/IV	Rec (2/96)/USA; prereg/ Europe, Canada/ colorectal cancer	
Immunomedics	LymphoScan, ImmuRAID-LL2-Tc-99m	Antibody fragment linked to ^{99m}Tc-labeled/IV	Phase III/USA, Canada/ imaging for lymphoma	Licensing agreement with Pharmacia was terminated in August 1995
NeoRx/Du Pont Merck (marketing NA); Boehringer Ingelheim (BI; marketing outside NA)	Nofetumomab merpentan/ NR-LU-10/Verluma (formerly OncoTrac)	Fab' fragment of NR-LU-10 MAb linked to ^{99m}Tc	PLA (3/94); rec (14/12)/ USA/sclc staging	BI's subsidiary, Dr. Karl Thomae will manufacture the product for WW use
Washington U School of Medicine, Department of Surgery		Copper-64-labeled BAT-2IT-1A3-F(ab')2, optimized to reduce renal uptake, imaged by PET	Phase I/advanced rectosigmoid cancer	Philpott GW, etal, Journal of Nuclear Medicine, 1995 Oct, 36(10): 1818-24

Abbreviations Key:
b *– began,* ***c*** *– completed,* ***rec*** *– recommended,* ***A*** *– approved,* ***L*** *– launched,* ***reg*** *– registered,* ***prereg*** *– preregistered*

Asia. High incidence rates are also encountered in China, Iran, former USSR nations (Turkmenistan, Kazakhstan, & Uzbekistan), Hong Kong, France, Argentina, and Japan. In most world regions, incidence is threefold higher in males, than in females, but the disparity is less pronounced in the former USSR. Karakalpakstan (Central Asia) is the only nation reporting higher incidence in females than in males.

Geographical variations in incidence have been attributed to various etiologic factors. The role of tobacco and alcohol in the development of esophageal cancer has been well established as an etiologic factor in the development of esophageal cancer in Western countries. High incidence in France and among blacks in the USA is associated with the combined effects of smoking and high alcohol consumption. In Central Asia and the former USSR, vitamin deficiency has been implicated as the major risk factor. Other possible factors that have been associated with increased incidence in Eastern countries include the use of opium, and consumption of hot tea, pickled vegetables, and foods with high levels of carcinogenic nitrosamines.

Mortality rates for esophageal cancer are uniformly very high, with the ratio between incidence and death ranging from 67% to 85%. In the USA overall five-year survival rates for esophageal cancer are merely 10%; the rate for metastatic esophageal cancer is 1.8%.

Drug Approval

QLT PhotoTherapeutics (formerly Quadra Logic Technologies; Vancouver, BC, Canada) received FDA approval in December 1995 to market its Photofrin (porfimer sodium) photodynamic therapy approach for the management of advanced refractory esophageal cancer (see FO, V1 #1, p 29; #2/3, p 56 & 64; and #4, pp 101-102). In the USA Photofrin was recommended for approval by ODAC in September 1994. Photofrin is currently approved in the USA, Japan (since 1994), Canada (in July 1995) and the Netherlands and France (1996) for esophageal cancer. Applications for marketing approval have also been filed in several European countries in 1995. In addition to the esophageal cancer indication, Photofrin is approved in Canada for the treatment of superficial bladder cancer; in France, the Netherlands and Japan for lung cancer; and also in Japan, for gastric and cervical cancer as well as cervical dysplasia.

In December 1995, QLT exercised an existing option and re-acquired from American Cyanamid marketing and distribution rights to Photofrin in all jurisdictions except Japan. In January 1996, QLT signed an agreement with Sanofi Winthrop granting the latter exclusive marketing rights in the USA, to Photofrin and benzoporphyrin derivative (BPD), a second generation photosensitizer, as well as other light-activated compounds. The agreement involves an access fee of $10 million comprised of a preferred stock purchase and cash and mile-

stone payments of $16.5 million based on approvals of Photofrin for other indications such as lung and head and neck cancer and Barrett's esophagus. Photofrin is being marketed in Canada by Ligand Pharmaceuticals (San Diego, CA) and in Japan, where it is approved for esophageal, gastric, lung and cervical cancer, by Lederle Japan, a joint venture between American Home Products and Takeda (Osaka, Japan). QLT is to receive between 26% and 29.5% of Photofrin sales in Japan. In 1995, sales of Photofrin in Japan were $167,334, reflecting lack of government reimbursement for the procedure. However, the drug will be reimbursed in Japan as of April 1996 at 213,000 yen ($2,000) per vial. The cost per treatment is estimated at $4,000 because, on the average, two vials are required per therapeutic regimen. The product has yet to be launched in markets outside Japan.

Exhibit 2
Incidence and Mortality of Esophageal Cancer by Gender in Selected World Regions in 1995

Country	Male		Female		Total		Total	
	Incidence (#)	Rate*	Incidence (#)	Rate*	Incidence (#)	Rate*	Mortality (#)	Rate*
Netherlands	783	10.2	438	5.6	1,221	7.9	943	6.1
Spain	1,694	8.7	363	1.8	2,057	5.2	1,701	4.3
Italy	2,224	8.0	881	3.0	3,106	5.4	2,335	4.1
Germany	3,543	8.9	1,379	3.3	4,922	6.0	3,945	4.8
United Kingdom	3,475	12.2	2,531	8.5	6,006	10.3	3,981	6.8
France	6,049	21.4	891	3.0	6,941	12.0	4,837	8.3
Other EEC	1,665	8.6	810	4.0	2,475	6.3	1,900	4.8
Total Western Europe EEC	19,434	11.4	7,293	4.1	26,728	7.6	19,642	5.6
Total Western Europe-non EEC	1,111	6.6	502	2.9	1,613	4.7	1,293	3.8
Poland	1,271	6.8	492	2.5	1,764	4.6	1,285	3.3
Other Eastern Europe	2,566	7.5	745	2.1	3,311	4.7	2,348	3.3
Total Eastern Europe**	3,837	7.2	1,237	2.2	5,075	4.7	3,633	3.3
TOTAL EUROPE**	24,382	10.1	9,033	3.6	33,415	6.8	24,568	5.0
Turkmenistan	866	49.9	619	34.6	1,484	42.1	875	24.8
Ukraine	2,149	9.0	743	2.7	2,892	5.6	2,220	4.3
Kazakhstan	2,009	25.2	1,537	18.1	3,546	21.5	2,044	12.4
Uzbekistan	2,231	22.8	1,384	13.8	3,614	18.2	1,186	6.0
Russia	7,239	10.5	3,512	4.5	10,752	7.3	9,029	6.1
Other USSR	1,924	8.5	789	3.2	2,713	5.7	1,634	3.4
TOTAL FORMER USSR	16,419	12.2	8,583	5.7	25,001	8.8	16,989	5.9
Canada	937	6.3	382	2.5	1,319	4.4	1,194	4.0
United States	9,400	7.3	2,900	2.2	12,300	4.7	11,200	4.3
TOTAL NORTH AMERICA	10,337	7.2	3,282	2.2	13,619	4.6	12,394	4.2
New Zealand	172	9.8	85	4.7	257	7.2	218	6.1
Hong Kong	478	17.0	117	4.3	595	10.8	366	6.6
Australia	704	7.8	408	4.5	1,112	6.1	841	4.6
Argentina	3,141	18.5	493	2.8	3,634	10.5	2,024	5.9
Japan	8,228	13.4	1,847	2.9	10,075	8.1	8,770	7.0
TRIAD (EUROPE, JAPAN AND NORTH AMERICA)**	42,948	9.6	14,162	3.0	57,110	6.3	45,733	5.0

** Per 100,000 population*
*** Excluding the former USSR*

Exhibit 3
Overall Incidence, Incidence of Advanced Disease and Mortality of Colorectal Cancer Worldwide in 1995

Country	Rate	Incidence (#)	Rate	Mortality (#)	Advanced Stage at Diagnosis (#)
Luxembourg	52.1	212	29.3	119	54
Ireland	43.4	1,542	24.8	881	393
Greece	17.6	1,843	12.3	1,290	470
Denmark	62.6	3,241	40.3	2,088	826
Portugal	35.2	3,460	21.9	2,148	882
Belgium	58.6	5,926	32.5	3,285	1,511
The Netherlands	49.5	7,674	26.1	4,049	1,957
Spain	30.1	11,907	18.9	7,503	3,036
France	46.8	27,138	28.5	16,553	6,920
United Kingdom	54.5	31,732	33.4	19,455	8,092
Italy	58.1	33,234	24.0	13,735	8,475
Germany	50.4	41,124	36.7	29,980	10,487
Total EEC	48.3	169,033	28.9	101,086	43,103
Finland	30.8	1,571	19.3	984	401
Norway	58.8	2,550	34.6	1,499	650
Switzerland	52.6	3,787	28.7	2,066	966
Austria	59.4	4,735	35.6	2,837	1,208
Sweden	55.3	4,855	28.9	2,537	1,238
Total non-EEC[1]	51.9	17,655	29.5	10,024	4,502
Slovenia	28.6	556	15.0	292	142
Slovakia	33.9	1,814	18.8	1,005	463
Bulgaria	36.2	3,176	21.5	1,882	810
Yugoslavia	29.9	3,239	15.2	1,649	826
Hungary	32.9	3,323	41.4	4,192	847
Romania	16.3	3,717	11.4	2,600	948
Czech Republic	51.5	5,305	34.9	3,598	1,353
Poland	21.0	8,049	17.0	6,523	2,052
Total Eastern Europe	26.9	29,178	20.0	21,741	7,440
TOTAL EUROPE[2]	43.9	215,865	27.0	132,851	55,046
FORMER USSR	31.6	90,152	16.3	46,638	22,989
Singapore	27.0	730	14.8	400	186
Chile	8.9	1,179	5.7	748	301
Israel	35.4	1,431	15.7	634	365
Cuba	15.4	1,502	12.7	1,239	383
Hong Kong	31.3	1,729	14.9	821	441
New Zealand	58.3	2,085	30.5	1,090	532
Australia	49.7	8,998	25.1	4,540	2,295
Argentina	27.5	9,498	13.9	4,801	2,422
Japan	39.5	49,474	22.3	27,841	12,616
Canada	54.5	16,300	20.7	6,200	4,157
United States	50.7	133,500	20.9	54,900	34,051
TOTAL NORTH AMERICA	51.1	149,800	20.8	61,100	38,208
EUROPE[2]**, NORTH AMERICA & JAPAN**	45.6	415,139	24.4	221,792	105,869

[1]Includes Iceland and Malta. [2]Excluding the former USSR

COLORECTAL CANCER

Epidemiology Update

Approvals of novel chemotherapeutics for the treatment of advanced colorectal cancer, have also brought into focus this common cancer which was diagnosed in approximately 106,000 patients in Europe (excluding the former USSR), North America and Japan, based on a total incidence of colorectal cancer of approximately 415,000 in these regions (see Exhibit 3).

Drug Approvals

The two new drugs approved for the treatment of colorectal cancer overseas are Zeneca's thymidylate synthase (TS) inhibitor Tomudex (raltitrexed or ZD1694) and Rhône-Poulenc Rorer's topoisomerase I inhibitor Campto (irinotecan). Tomudex was approved in the UK in August 1995, as first-line treatment of advanced colorectal cancer and Campto was approved in France as second-line treatment for advanced colorectal cancer refractory to conventional treatment. [Another topoisomerase I inhibitor, topotecan hydrochloride (Hycamtin; SmithKline Beecham) was recommended for approval in the USA by ODAC in April 1996 for metastatic ovarian cancer].

These drugs are to compete with combination therapy using 5-fluorouracil (5-FU) and levamisole or other 5-FU combinations (see FO, V1 #2/3, pp 47-49). These newly-approved drugs will create a new market for chemotherapeutic agents to treat colorectal cancer, to date dominated by 5-FU, a low-cost generic drug.

Zeneca's Tomudex is the first new drug to compete with 5-FU and combinations in the treatment of advanced colorectal cancer. It is a highly specific TS inhibitor with a more favorable toxicity profile, and is more active and more convenient to administer than 5-FU. The drug is also being clinically evaluated in pancreatic, ovarian, breast and head and neck cancer and nsclc, and in various combination therapies.

Rhône-Poulenc Rorer's Campto (CPT-11) was launched in France in September, 1995. RPR licensed irinotecan from Yakult Honsha/Daiichi that launched the drug as Topotecin in Japan, its first market, in April 1994, for sclc, nsclc, and cervical and ovarian cancer. In a large European study involving 213 chemotherapy-naive and pretreated patients, response rate in evaluable patients was 20.5%. The main toxicities associated with irinotecan therapy are neutropenia and severe diarrhea. Prophylaxis with antibiotics is used to prevent infections whereas various drugs, such as high-dose loperamide and kampo (a Chinese herb) are being employed to treat diarrhea that appears to be induced by hyperplastic metamorphosis of the intestine caused by CPT-11, as was demonstrated in animal models. Kampo which contains a β-glucoronidase (baicalin) antagonist, acts to reduce intestinal concentrations of SN-38, the active metabolite of CPT-11 (Ikuno N, etal, J NCI, Dec 20, 1995, 87 (24): 1876-1883).

MECHANISMS IN MALIGNANCY

APOPTOSIS

New Findings

Induction of apoptosis remains the target of many therapeutic approaches in cancer and is being employed as an end point in establishing efficacy during preclinical evaluation of anticancer agents. Induction of apoptosis has been associated with many conventional chemotherapeutics but the exact mechanism for such activity has not been always elucidated. Tamoxifen (Nolvadex; Zeneca), a widely used anticancer agent with activity against both estrogen-receptor (ER) positive and negative cancers, was shown to induce apoptosis in various malignant cell lines *in vitro*. Tamoxifen is thought to induce apoptosis in ER-positive cells via hormone deprivation. Apoptosis observed in tamoxifen-treated ER-negative cells may be mediated through an overexpression of c-myc. Treatment of malignant breast cells with tamoxifen *in vitro* for 72 hours increased c-myc mRNA five-fold, c-Myc protein threefold and resulted in apoptosis (Kang Y, J NCI, Mar 6, 1996, 88(5):279-284).

A surprise finding was reported by researchers at Lund University (Sweden) who discovered that human milk killed lung cancer cells *in vitro.* Analysis revealed that a milk component (multimeric alpha-lact-albumin) elevates Ca^{2+} and induces apoptosis.

Apoptosis Technology (ATI), a subsidiary of ImmunoGen (Cambridge, MA), in collaboration with researchers at St. Louis University Medical Center, reported that it discovered, cloned and analyzed a new protein, Bik (Bcl-2 interacting killer) which promotes apoptosis. Bik interacts with the cellular survival-promoting proteins, Bcl-2 and Bcl-xL, as well as the viral survival-promoting proteins, Epstein Barr virus-BHRF1 and adenovirus E1B-19 kDa. Bik promotes apoptosis in a manner similar to members of the Bcl-2 family, Bax and Bak (Boyd JM, etal, Oncogene, 1995 Nov 2, 11(9):1921-8). Based on these findings ATI is planning to develop antiviral drugs. It is theorized that one mechanism by which viruses survive is by de-activating Bik. Restoring the natural function of Bik may prevent viruses from spreading. ATI's first target is human cytomegalovirus (CMV). In a related development, ATI also reported that it discovered a key region, BH3, in Bak (EMBO Journal, 1995, 14:5589-5596). ATI is using BH3 to identify anticancer and antiviral compounds.

Apoptosis Mediating Drugs in Development

Milkhaus Laboratory (Boxford, MA) initiated, in April 1996, a phase I clinical trial of LDI-200, a formulation of chorionic gonadotropin which mediates apoptosis, for the treatment of solid tumors. In October 1995 this product also entered a phase I clinical trial in refractory leukemia. An IND to investigate LDI-200 in cancer pain was also approved.

ANGIOGENESIS

Research in tumor angiogenesis is proceeding along both diagnostic and therapeutic lines. However, considerable controversy surrounds both applications.

Angiogenesis in the Assessment of Cancer

Implication of angiogenesis as a key contributor to tumor progression and metastasis has led researchers to use angiogenesis as a marker in the detection and monitoring of cancer (see FO, V1 #7/8, pp 195-199). Two clinical applications in the cancer area, currently investigated based on quantifying angiogenesis, are patient prognosis and tumor responsiveness to anticancer therapy.

Although there is considerable controversy surrounding the prognostic value of angiogenesis, several investigators reported encouraging results using angiogenesis-based patient prognosis in breast cancer (see FO, V1 #7/8, p 254) and other malignancies. Assessment of intratumoral microvessel density (IMD) in primary breast cancer was shown to be a significant and independent prognostic marker (Gasparini G and Harris AL, Clinical Oncology 1995 Mar, 13 (3):765-82).

Investigators are currently seeking associations between angiogenic activity and metastasis and/or prognosis in other solid tumors, such as colorectal adenocarcinoma, head and neck squamous cell carcinoma and Kaposi's sarcoma. Although the microvascular supply in

primary and metastatic colorectal adenocarcinomas showed only moderate differences of overall vascular density between tumor tissue and surrounding colorectal mucosa, the presence of a collagen IV positive membrane was identified as a demarcation for more intense angiogenic response in the stroma. Vascular "hot spots", similar to those seen in breast cancer were also identified. There was low variablity in microvessel density (MVD), expressed as the number of vessels/X250 field, in different hot spots within the same tumor section whereas intertumor variability was significantly higher. Using a double staining technique, investigators observed a much higher percentage of cycling endothelial cells within the tumor compared with normal colon mucosa and adjacent mucosa (21% versus 0.59% versus 1.5%). Within tumors, regional differences in MVD correlated with differences in tumor cell proliferation. Expression of p53 also correlated to MVD (Dirix LY, ECCO8, Abs. 23). For instance, a majority (76%) of p53-positive tumors was highly vascular (>90 vessel/x200 field in the areas of intense neovascularization), with a mean MVD of 114 ±43, compared to only 31% of the p53-negative tumors, with a mean MVD of 104 ±50 (Vermeulen PB, ECCO8, Abs. 722).

Angiogenesis also may play a role in predicting effectiveness of anticancer treatments. Gasparini, etal, showed that IMD predicts clinical outcome in a series of 191 node-positive breast cancer patients treated either with adjuvant hormone therapy or chemotherapy with a median follow-up of 5 years. Also, IMD predicted objective response in 73 patients with stage II-IV head and neck cancer, treated with concurrent chemoradiation therapy.

Angiogenesis-based Therapeutics

Numerous agents are in preclinical development and several are being evaluated in clinical trials (see FO, V1 #7/8, Exhibit 11, pp196-198). It is generally believed that selective anti-angiogenic agents will be most effective when used in combination, either with other complimentary angiogenesis inhibitors or with conventional chemotherapeutics. In animal models of pancreatic cancer, a combination of three anti-angiogenic agents, Takeda's AGM-1470 (TNP-470), minocycline and interferon, reduced tumor growth by 89%. Parenthetically, anecdotal information on AGM-1470's effectiveness against refractory tumors is very favorable, but findings reflect experience with only a few patients. The drug is in phase II clinical trials in the USA. Because of the nature of anti-angiogenesis therapies, i. e. inhibition of an ongoing process, agents may need to be administered over long periods of time to prevent recurrence.

Angiogenesis Technologies (Angiotech; Vancouver, BC, Canada) which began operations in the fall of 1992, is developing vanadium compounds as angiogenesis inhibitors in cancer. In *in vitro* studies orthovanadate, at concentrations of 5 to 10 μM, was cytotoxic to proliferating but not quiescent cells. In animal studies tumor growth was inhibited by 80% to 100% when mice with solid tumors were administered orthovanadate or vanadyl sulfate, subcutaneously, for nine days (Cruz TF, etal, ASCO95, Abs. 2357).

EntreMed (Rockville, MD) and Bristol-Myers Squibb signed an agreement in December 1995 under which EntreMed gave BMS exclusive worldwide rights to both Angiostatin and its thalidomide analogs (see FO, V1 #7/8, p. 195) as well as first refusal rights to other potential antiangiogenic compounds under development by Dr. Judah Folkman's team at Children's Hospital (Boston, MA). In exchange, BMS made an equity investment in EntreMed, and agreed to fund a 5-year collaborative research effort to develop these anti-angiogenesis compounds for the treatment of cancer.

Texas Biotechnology (Houston, TX) has identified and is evaluating, in the research stage, a vascular endothelial growth factor antagonist, TBC1635, for its potential utility as an angiogenesis inhibitor for the treatment of cancer.

Other Developments

In October 1995, Human Genome Sciences (Rockville, MD) applied for world patents covering sequences of fibroblast growth factor FGF 10 and VEGF 2, and ImClone Systems (New York, NY) has applied for a worldwide patent covering MAbs to VEGF receptor.

ANTICANCER DRUGS AND MARKETS

TAXANES

Taxanes are proving the blockbuster oncology drugs of the 1990s (for a comprehensive review of the worldwide status of taxanes, in terms of products, developers, indications, clinical trials and markets see FO, V1 #7/8, pp 175-185).

Paclitaxel

Global revenues of paclitaxel (Taxol; Bristol-Myers Squibb) rose 68% in 1995 to $580 million from $340 million in 1994, representing about 73,500 treatment regimens worldwide. Sales increased 59% in the first quarter of 1996, to reach $200 million. The drug is expected to surpass $750 million in global sales in 1996. Future growth will come from expanded indications and new geographic markets. Taxol is expected to be approved as first-line treatment in ovarian cancer and to be launched in its last market, Japan, in 1996. In February 1996, Bristol-Myers Squibb (BMS) extended its agreement with Indena (Milan, Italy), BMS' main supplier of the paclitaxel intermediate 10-deacetylbaccatin III since 1992, to 2000.

Docetaxel

Rhône-Poulenc Rorer launched Taxotere in France and Portugal in early 1996 for anthracycline-resistant breast cancer. The drug is currently approved in over 22 markets overseas for this and other indications and is being sold in seven. It has been recommended for approval in the USA (see V1, #7/8. pp 179, 181 and 183). Taxotere is also being evaluated in combination with Adriamycin, cyclophosphamide and tamoxifen (ACT) by the National Adjuvant Breast and Bowel Project, as a pre-operative regimen in 1,500 women with breast cancer. End-points are disease-free and overall survival.

PLATINUM-BASED DRUGS

Revenue growth of platinum-based drugs exceeded expectations. Estimated worldwide sales of cisplatin (Platinol; Bristol-Myers Squibb) were $165 million in 1995, posting a 6.5% growth over 1994 levels. In the USA sales of Platinol rose 4.2 % in 1995 to $125 million from $120 million in 1994. Platinol's patent expires in the USA in December 1996. Sales of cisplatin benefited from increased use in combination with taxanes (see FO, V1 #7/8, p 184). Sales of carboplatin (Paraplatin; Bristol-Myers Squibb) posted an even higher 18.5 % growth rate, rising from $275 million in 1994 to $320 million in 1995. USA sales of carboplatin were $180 million in 1995 compared to $140 million in 1994, posting a growth rate of 28.6%.

JM-216

The oral platinum-based agent, JM-216, under joint development by the Institute of Cancer Research (UK), Bristol-Myers Squibb and Johnson Matthey, exhibits a similar spectrum of activity as carboplatin. It has demonstrated antitumor activity in phase I trials in ovarian cancer, sclc, nsclc, and mesothelioma (see FO, V1 #7/8, p 174) and is now in phase II. The recommended dose for phase II studies is 100-120 mg/m²/day for five days. The dose-limiting toxicity is myelosuppression.

TECHNOLOGY UPDATE

RADIOPHARMACEUTICALS IN CANCER DIAGNOSIS

The diagnostic radiopharmaceuticals market is being rejuvenated worldwide with opportunities emerging among many applications within such diverse areas as cardiovascular disease, infection, neurology and cancer. This report is based on a new comprehensive market research and technology assessment study entitled, *The U.S. Market for Diagnostic Radiopharmaceuticals*, issued by New Medicine in May 1996.

USA Markets

Market estimates and forecasts. The USA market for diagnostic radiopharmaceuticals grew from about $300 million in 1991 to $477.2 million in 1995 and is expected to reach $1,051 million in 2000 (see Exhibit 4). Although most historic market growth is attributed to increases in the cardiovascular segment of the market, future growth will be shared by both sectors, with the general nuclear medicine segment increasing from $157 million in 1995 to $396 million in 2000. Among products within this latter segment are various radiopharmaceutical preparations used in the diagnosis, staging and monitoring of cancer. Although cancer applications account for only a part of several of these markets, they represent important growth segments. Other growth markets include functional organ studies and diagnostic imaging in infectious and neurologic diseases.

DuPont Merck Pharmaceuticals (Wilmington, DE and North Billerica, MA) is the leading manufacturer of radiopharmaceuticals, controlling 58.6% of the USA market in 1995, followed by Mallinckrodt (St. Louis, MO), Amersham/Medi-Physics (Arlington, IL), Fujisawa Pharmaceutical (Deerfield, IL) and Bracco (Princeton, NJ), in that order.

Distribution trends. In 1995 the bulk of radiopharmaceuticals revenues (76.6%) was channeled through centralized radiopharmacies and the remainder was sold directly to hospitals. There were 242 nuclear pharmacies in 1995 with 45% owned by Syncor (Chatsworth, CA). The two other radiopharmacy owners are Amersham Medi-Physics and Mallinckrodt with the remaining being independently owned. Syncor is the largest distributor controlling 64.9% of USA revenues. As of June 1995, DuPont Merck Pharmaceuticals began shipping all of its radiopharmaceutical products exclusively through Syncor.

Pricing trends. In the cancer detection and imaging sector, prices per dose for radiopharmaceuticals range from $4.75 for commodity products such as MDP used in bone scans, to $350 for OncoScint and $800 for Octreoscan. New agents are expected to command high prices.

Agents Approved, Recommended or in Development for Cancer Imaging

In the cancer area, particularly promising are novel cancer imaging approaches using either radioisotopes linked to peptides (see FO, V1 #6, pp 164-167) or radioimmunoconjugates (see FO, V1, #2/3, pp 65-72). Approvals of Cytogen's OncoScint CR/OV in 1992 and Mallinckrodt's Octreoscan in 1994 were milestones for nuclear medicine, ushering a stream of new products and expanding indications. This article updates information presented in previous FUTURE ONCOLOGY issues. New agents and changes in the status of agents previously reported in FUTURE ONCOLOGY are presented in Exhibit 1. In addition to the profiles of several companies that follow, many others participate in this market, including IDEC Pharmaceuticals (see FO, V1 #11, p 244), PerImmune (see FO, V1 #2/3 p 71), Mallinckrodt Medical and CIS-US (FO, V1 #6, p 167), among others.

Antisoma (London, UK), organized in August 1990 as a mediator for drug discoveries between academia and the pharmaceutical industry, owns a group of patented anti-idiotypic antibodies and peptides with diagnostic and therapeutic potential for various cancers. Some of the company's patents have been licensed from the Imperial Cancer Research Fund (ICRF; London, UK). One agent under development is AS 109, a technetium-labeled synthetic pentadecapeptide (alpha M2) derived from the third heavy-chain complementarity-determining region (CDR-3H) of a tumor-associated MAb, directed against the pan-carcinoma cell-surface antigen, polymorphic epithelial mucin. In 1995 Antisoma and the Royal Postgraduate Medical School at Hammersmith Hospital (London, UK) reported phase I clinical results of AS 109, in 26 women with primary, recurrent, or metastatic breast cancer. Breast tumors and metastases were visualized shortly after administration (optimal at 3 hours) of the agent. Overall, 57 (77%) of 74 sites were visualized. Fourteen of 15 primary tumor sites and all of eight local recurrences were successfully imaged as well as five of six metastases in the opposite breast, eight of 15 metastatic axillary lymph nodes, and all of six metastatic supraclavicular lymph nodes. Metastatic sites in the lungs, mediastinum, chest wall, and liver were poorly visualized because of background cardiac blood pool. Alpha M2 detected small lesions (< 2 cm) as efficiently as larger ones. The peptide was rapidly (3 hours) cleared from the circulation. No acute or chronic adverse reactions were attributed to alpha M2 (Sivolapenko GB, etal, Lancet, 1995 Dec 23-30, 346(8991-8892):1662-6). Phase II clinical trials are underway in the imaging of primary, recurrent and metastatic breast, stomach, colon and ovarian cancer. Antisoma is also collaborating with Sumitomo's (Tokyo, Japan) Nihon Medi-Physics subsidiary (Amersham also has a 20% stake in this company) on a variant of AS 109 for the diagnosis of gastrointestinal cancer.

Exhibit 4
Historic and Forecast USA Markets of Radiopharmaceuticals in Cancer Diagnosis and Related Areas

Products	1995 Market ($ mil.)	2000 Market ($ mil.)	CAGR (%)
Technetium Generators*	35.0	46.6	5.9
Technetium Kits*	38.0	39.4	0.7
MDP, HDP/Bone Scans	10.0	10.7	1.4
DTPA-Kidney/Brain Scans	2.8	3.0	1.4
Sulfur Colloid/Liver (functional)*	2.0	2.0	—
Hepatolite, Cholotec/Biliary (functional)*	8.0	8.5	1.2
MAG 3/Kidney (functional)*	15.2	15.2	—
Cancer Imaging (MAbs and peptides)	11.5	184.2	74.1
Octreoscan	10.1	16.3	10.0
OncoScint CR/OV**	1.4	—	—
New Agents	0.0	167.9	—
Iodine Products*	13.5	14.8	1.7
Iodine 131	7.2	7.7	1.4
Iodine 123	6.3	7.1	2.4
Indium Chloride/Tumor Imaging*+	2.4	39.2	74.8
Other Isotopes*	5.6	6.1	1.7
General Nuclear Medicine Products*	157.1	396.3	20.3
ALL RADIOPHARMACEUTICALS *	$477.2	1,051.4	17.1

** Used in many other applications outside cancer ** To be replaced by new agents + Excluding Octreoscan*
Source: The U.S. Market for Diagnostic Radiopharmaceuticals, published by New Medicine, May 1996

Biomira (Edmonton, Alberta, Canada) is developing the Tru-Scint line of diagnostic immunoconjugates for imaging various tumors. Tru-Scint AD kit is a lyophilized (freeze-dried) preparation of MAb 170 which binds most adenocarcinomas, linked to ^{99m}TC. Tru-Scint AD is being evaluated in a pivotal, multicenter, open label, phase II/III clinical trial which started in the USA in October 1995, to confirm its efficacy in localizing recurrent breast cancer. Because MAb 170 also binds to cancer cells other than breast cancer, Tru-Scint AD is being evaluated, in phase II trials, in ovarian and colorectal cancers. A phase III clinical trial with Tru-Scint AD is being planned for ovarian cancer.

Cytogen's (Princeton, NJ) OncoScint CR/OV, although on the USA market for the past three years, has failed to capture a significant market share, with domestic sales hovering about $1.4 million annually. In the meantime, the company forged new marketing alliances as past collaborators exited the scene. An agreement with Knoll to market OncoScint CR/OV in the USA, entered in 1991, was dissolved in 1994, leaving Cytogen the sole distributor of its product in the USA. A similar disengagement agreement was executed with Chiron (Emeryville, CA) in 1994, reverting the rights to the European market to Cytogen. Subsequently, Cytogen entered agreements with Faulding (Adelaide, South Aus-

tralia), in December 1995, and CIS bio international (Gif-sur-Yvette Cedex, France), in January 1996, to market and distribute OncoScint CR/OV outside the USA. In November 1995, the FDA approved repeat administration of OncoScint, thus removing a serious limitation regarding clinical use of the agent. OncoScint is also being evaluated in breast cancer and another Cytogen imaging agent, ProstaScint, for detection and staging of prostate cancer, is under FDA review.

Diatide (formerly Diatech; Londonderry, NH) entered into a non-exclusive distribution agreement with Syncor that allows the latter to market Diatide's somatostatin-receptor binding peptide, Techtide P829, in Hong Kong and Tawain. ^{99m}Tc-labeled Techtide P829, a follow-up to Diatide's P587, is in phase III clinical trials for imaging tumors that express somatostatin receptors (also see FO, V1 #6, p 167). In August 1995 Nycomed Imaging (Princeton, NJ) entered into an exclusive licensing agreement (with a five-year option) to market Diatide's products in Europe, Africa and the Middle East, as well as co-promote them in the USA. As part of the agreement Nycomed made a $10 million equity investment in Diatide, and will also provide significant R&D funding, make milestone payments and pay an option fee and royalties on sales.

DuPont Merck Pharmaceutical is the leading manufacturer of radiopharmaceuticals in the USA. The company's cardiovascular agent, Cardiolite (sestamibi), approved for heart perfusion studies, has been one of the most successful radiopharmaceuticals introduced in the USA market to date. Sales of Cardiolite rose from $25 million in 1991 to $112.8 in 1995 and are expected to reach $187 million in 2000. Cardiolite, under the brand name Reluma, is also being investigated in imaging cancer. Although the exact mechanism of cellular uptake of sestamibi in cancer cells has not been elucidated, recent data suggest that 90% of the tracer's activity is concentrated in the mitochondria.

DuPont recently sponsored a large multi-center trial to assess the efficacy of Reluma in diagnosing breast cancer. An important study objective was to determine Reluma's sensitivity and specificity in distinguishing malignant from benign lesions, attributes that would confer the agent a distinct advantage over mammography. Although mammography is very sensitive in the detection of breast abnormalities it often cannot be used to accurately differentiate between benign and malignant tissue. Because, statistically, 75% of women who undergo biopsy have benign lesions, nuclear medicine appears to offer an additional option to improve diagnostic sensitivity, particularly in women with dense breasts, or scarring from previous lumpectomy. One of the largest clinical trials was performed at UCLA (Los Angeles) where 147 consecutive patients were evaluated with scintimammography. Results indicated a sensitivity of 92.2%, a specificity of 89.2%, a positive predictive value of 81.0% and a negative predictive value of 95.8%, in detecting primary carcinoma of the breast.

Immunomedics' (Morris Plains, NJ) CEA-Scan was recommended for approval, in February 1996, by FDA's Medical Imaging Drugs Advisory Committee as a diagnostic tool in conjunction with other standard diagnostic tests to detect recurrent colorectal cancer by confirming CT-negative results or locating additional metastatic sites. CEA-Scan comprises a murine MAb fragment (Fab') against CEA, labeled with ^{99m}Tc. The small MAb fragment is delivered at a low dose virtually eliminating the risk of serious HAMA (human antimouse antibody) reaction.

The agent is also awaiting approval in Europe. Immunomedics is also planning to commence clinical trials and seek regulatory approval of CEA-Scan in Japan. Immunomedics re-acquired North American marketing rights, obtained in July 1991, from Pharmacia & Upjohn in August 1995. Immunomedics has entered into an agreement with Mallinckrodt Medical BV, based in the Netherlands, to market and distribute CEA-Scan in Western Europe and certain countries in Eastern Europe. Immunomedics will manufacture CEA-Scan for Mallinckrodt.

CEA-Scan is also in phase III clinical trials for lung cancer and in phase I/II for breast cancer. In March, 1996, Immunomedics reported that in a phase II clinical trial of 27 women with breast cancer, conducted at the University of Miami Cancer Center, CEA-Scan demonstrated accuracy of 81% and sensitivity of 89% for revealing cancers in the breast, as compared to surgical findings. The agent also detected axillary lymph node metastases. Other indications for CEA-Scan include esophageal, medullary, thyroid, lung, stomach, bile duct, pancreatic, ovarian, uterine and cervical cancer.

Other Immunomedics cancer imaging agents in development are LymphoScan and AFP-Scan, both designated orphan drugs. A phase III clinical trial of LymphoScan for staging non-Hodgkin's lymphoma is under planning. The company will conduct clinical trials of AFP-Scan in liver cancer outside the USA, probably in Japan, where this cancer is more prevalent.

In 1995 Immunomedics was also issued a Notice of Allowance by the U.S. Patent and Trademark Office for a patent application of a method of quantitatively labeling an antibody fragment with ^{99m}Tc at the treatment site in 5 minutes. An interference with regard to a similar patented process by RhoMed (Albuquerque, NM) was resolved when the latter's patent was reissued with a modification. A patent was also issued to the company covering a pretargeting method incorporating a large polymer that increases the binding sites at the target.

Neoprobe (Dublin, OH) signed an agreement with Syncor in October 1995, under which Syncor will market Neoprobe's RIGScan CR49 product line in the USA (see FO, V1 #2/3, p 72). In December 1995, a similar agree-

ment was signed with Nordion Europe to distribute this product in Europe, Africa and the Middle East. The agreement with Nordion, the solitary supplier of iodine-125, also ensures Neoprobe with an ongoing source of this isotope. Bulk manufacturing of CR49 for RIGScan has been assigned to Bio-Intermedair BV (Netherlands) which has already received clearance for bulk antibody production from the Dutch and European Health Ministries. Final vialing and filling will take place at Neoprobe's wholly-owned subsidiary, NewMonoCarb AB (Lund, Sweden). Nordion International (Kanata, Ontario, Canada) will perform the radiolabeling of RIGScan CR49 for North American manufacturing and Neoprobe's subsidiary in Israel (a joint venture with Rotem Industries, the private arm of the Israeli Atomic Energy Commission) will manufacture the product for European distribution. Nordion is currently supplying RIGScan CR49 to phase III clinical trials sites in the USA and Europe. The Israeli subsidiary will construct and operate a state-of-the-art radiolabeling facility which is planned to be operational in the third quarter of 1996.

RIGScan CR49 has just completed phase III trials for intra-operative detection of colorectal cancer. Other RIGScan indications in development are RIGScan BR which uses both a MAb and peptide agent, for breast cancer; RIGScan OV, which uses a MAb as well as an antibody fragment, for ovarian cancer; and RIGScan NE which employs a peptide analog, for neuroendocrine/endocrine cancers. Neoprobe also announced preliminary results with its adoptive cellular therapy (ACT) which is in phase I/II clinical trials for treatment of late stage colorectal cancer. These results have encouraged Neoprobe to prepare for the next stage of clinical testing of RIGS/ACT. In RIGS/ACT the surgeon removes lymph nodes identified by the RIGS system. Immunologically active "helper" cells, present in these lymph nodes, are activated *ex vivo* and multiplied in a short-term processing step. Once re-injected, these cells are expected to boost the patient's own immune system to fight the cancer.

NeoRx (Seattle, WA) is awaiting FDA decision on its cancer imaging agent, Verluma (^{99m}Tc nofetumomab merpentan). In December, 1995, ODAC recommended that Verluma be approved for the initial staging of patients with biopsy-confirmed small cell lung cancer (sclc). Verluma is composed of a MAb fragment linked to ^{99m}Tc that targets and localizes in tumor tissues that express a specific tumor marker. Patients are imaged by gamma camera 14 to 17 hours after administration of the agent.

DuPont Merck Pharmaceutical holds the exclusive rights to market Verluma in North America. Boehringer Ingelheim has the right to market Verluma outside North America and its wholly-owned subsidiary, Dr. Karl Thomae (Biberach an der Riss, Germany), will manufacture of Verluma for worldwide distribution. NeoRx has also developed Avicidin (see FO, V1 #2/3, pp 69-70), a pretargeting technology that prevents "innocent bystander" toxicity associated with the administration of conventional radiopharmaceuticals.

Boehringer Ingelheim (Ridgefield, CT) filed a PLA in March 1994, based upon data from a pivotal phase III study involving 89 patients, showing that Verluma provides overall staging accuracy similar to a battery of four traditional tests (CT-head, CT-abdomen, CT-chest and bone scan). A single fully blinded review of Verluma images correctly staged 82% of all newly-diagnosed sclc patients and 77% of patients with the more severe, extensive stage of the disease, with a positive predictive value of 94%; there were 13 (15%) false negatives for extensive disease. Identifying patients with extensive disease, for whom chest radiation therapy is of no value, may be an important contribution of Verluma. However, its role in initial staging of sclc will have to be determined by its clinical utility. Verluma was not superior when compared with any one currently employed imaging technique in the initial staging of sclc, but its overall performance in all organ systems may prove an advantage. Verluma, comprised of MAb fragments, was associated with a very low (<6%) rate of HAMA.

Nycomed Imaging, a business unit of Hafslund Nycomed (Oslo, Norway), is a leading manufacturer of medical diagnostic contrast agents worldwide (see FO, V1 #10, pp 237-238). In March 1996, Nycomed Imaging formed a new company, Isopharma (Oslo, Norway), with Norway's Institute of Energy Technology to develop radiopharmaceuticals.

Resolution Pharmaceuticals (Mississauga, Ontario, Canada), a joint venture formed by Allelix Biopharmaceuticals (Mississauga, Ontario, Canada) and Nordion International, a division of MDS Health Group (Etobicoke, Ontario, Canada), has entered into a research collaboration with AltaRex (Edmonton, Alberta, Canada). AltaRex will use Resolution's technetium imaging technology to develop cancer imaging agents.

Syncor International, is by far the largest USA distributor of radiopharmaceuticals, operating 119 radiopharmacies. Its recent affiliation with DuPont Merck Pharmaceutical, making Syncor the primary channel for DuPont's products has further solidified Syncor's position in this market. Syncor has several other affiliations as indicated above. In May 1996, Syncor and CTI Services (Knoxville, TN) formed a joint venture, P.E.T.Net Pharmaceutical Services, to develop radiopharmaceuticals for positron emission tomography (PET).

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