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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

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MEETING COVERAGE

ADVANCES IN THE MANAGEMENT OF GASTROINTESTINAL CANCER

FROM THE 62ND ANNUAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG) CHICAGO, IL; NOVEMBER 3-5, 1997

ADVANCES IN THE MANAGEMENT OF HEMATOLOGIC MALIGNANCIES

FROM THE 39TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY (ASH) SAN DIEGO, CA; DECEMBER 5-9, 1997

STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

UPDATE OF PROSTATE CANCER — PART I EPIDEMIOLOGY

This three-part series on prostate cancer is an update of the extensive review of this disease presented in FO, pp 282-297, 298-300, 302-328, 396-401. Exhibit 1 presents 1998 prostate cancer incidence and mortality statistics in selected world regions. Age-specific incidence is presented in Exhibit 2. These populations reflect cases of full-blown malignancy. Irrespective of the incidence of actual malignancy, the prevalence of latent cancer (Exhibit 3) is enormous, affecting nearly one in three men. Although the significance of this statistic is questionable because only a small percent of such latent cancers go on to become true malignancies in one's lifetime and, currently, it is not possible to reverse the course of latent cancer, one may view such latency as a potential target for prevention. Prostate cancer usually progresses slowly, allowing several years to pass before the malignancy becomes clinically significant. According to studies that assessed tumor doubling time, this growth may take 10 to 15 years (CA, A Cancer Journal for Clinicians 1997;47:273-287).

Incidence and mortality rates of prostate cancer worldwide have stabilized after a period of what appeared to be an epidemic of such cases, particularly in the West. Increases in incidence rate during this period coincided with aggressive screening of non-symptomatic populations.

Prostate cancer incidence varies significantly from region to region (see Exhibit 2) but the reasons for such variations has not been adequately explained. Testosterone levels and diet have been implicated but the connection remains tenuous. In a case-control study performed in Athens, Greece, blood samples of 52 patients with prostate cancer and 52 age- and town-of-residence-matched healthy controls (adjusted for age, height, body mass index and education), were analyzed for potential relationships between hormones and prostate cancer risk. Based on a

blind multiple logistic regression analysis of patient serum findings, there was significant inverse association with dihydrotestosterone and nonsignificant inverse association with estradiol and prostate cancer risk. There was a marginally positive association of testosterone levels and incidence of prostate cancer, but no association was observed with respect to sex hormone-binding globulin (Signorello LB, etal, Cancer Causes Control 1997 Jul 8:4 632-6).

Dietary factors such as a high consumption of animal products including red meats, eggs and dairy foods, have demonstrated the strongest and most consistent positive association with aggressive prostate tumors. Various studies have shown lycopene, the carotenoid found in tomatoes, alpha-tocopherol supplementation, and vitamin D, to be protective. Recent studies have focused on phytoestrogens and other phytochemicals which may influence prostate cancer by altering male sex hormone levels or actions. Percent body fat is another potential prostate cancer risk factor associated with androgen activity during growth and development (Giles G and Ireland P, Int J Cancer 1997 Suppl 10: 13-7).

USA Epidemiology

The impact of screening programs in the USA on incidence rate of prostate is illustrated in Exhibit 4. An increase in incidence rates was apparent by 1992, when screening for prostate cancer using PSA tests reached 18,000 tests per 100,000 men. Interestingly, an immediate drop in such incidence was noted two years later. Because PSA-testing detects prostate cancer ≥5 years earlier than diagnosis by symptom onset or digital rectal exam, a surge in such screening identified many more cancers than in previous years when such testing had not been as widespread. As expected, however, in 1998 new cases of full-blown prostate cancer reverted to pre-PSA screening levels, reaching a new plateau and discounting dire predictions of an epidemic. From 1994 to 1998, incidence of prostate cancer increased two-fold and then fell back to 1994 levels. The rise in incidence during the 1995-1997 period may be attributable not only to overall increased screening levels but expansion of such screening to include a new component of the population, namely African American men, who did not participate in such programs in the past.

USA incidence statistics may also serve as a means of elucidating any links between prostate cancer and ethnicity. Although such links may eventually be better understood using molecular epidemiology, actual incidence data indicates a wide discrepancy in age-adjusted prostate cancer incidence rates among various ethnic groups residing in the USA (Exhibit 5) in line with the wide variations encountered between these ethnic groups outside the USA (Exhibit 1). Any discrepancies between incidence rates among established ethnic groups residing in the USA or their own countries, may point to environmental and socioeconomic factors.

One group particularly at risk, African American men, exhibit a 47% higher prostate cancer incidence and a 128% higher mortality. However, although higher incidence rates may be inherent, higher mortality rates maybe attributable to diagnosis when disease is at an advanced stage. According to a logistic regression analysis of associated histologic grade (high=poorly or undifferentiated versus low=well or moderately differentiated) and race (black versus white) of 4,114 cases of prostate cancer (1,380 blacks and 2,734 whites) in the Chicago area, adjusted for stage (localized, regional, and distant), the odds of high histologic grade prostate cancer in blacks was significantly higher (OR=1.7) when compared to whites. This may explain, in part, the higher mortality rate from prostate cancer encountered in African Americans (Freeman VL, etal, Prostate 1997 Feb 1 30:2 79-84).

Unlike the pronounced ups and downs in incidence rate, mortality rates from prostate cancer have risen steadily from 22.1 per 100,000 population in 1976 to an estimated 29.9 in 1998 (Exhibit 6). In the past decade the mortality rate rose 8.3%.

CANCER OF THE CENTRAL NERVOUS SYSTEM — PART III

NOVEL THERAPEUTIC APPROACHES

Despite the relative rarity of CNS malignancies, numerous agents are in development in this area (Exhibit 7). Although some of these agents address a variety of other solid tumors, many exclusively target CNS cancer and, particularly, brain cancer with its added unique challenge of the almost impenetrable blood-brain barrier (BBB).

NOVEL CHEMOTHERAPEUTICS

Numerous chemotherapeutics, among them commercial agents approved for other indications, discussed in Part II of this article, and novel agents, are being evaluated alone or in combination for the treatment of CNS malignancies.

9-aminocamptothecin (9-AC)

9-aminocamptothecin is being developed by IDEC Pharmaceuticals (San Diego, CA) for a variety of cancer indications. In phase II clinical trial (protocol IDs: CCF-IRB-1104, NCI-T94-0166D), sponsored by the NCI, and being conducted at Cleveland Clinic (Cleveland, OH), 9-AC is being investigated in the treatment of adult glioblastoma multiforme (GBM). Up to 28 patients will be accrued over 12-18 months and treated pre-irradiation with 9-AC and Amgen's (Thousand Oaks, CA) granulocyte-colony stimulating factor (G-CSF). For more on 9-AC see FO, p 539.

Alanosine

Alanosine, under development by Triangle Pharmaceuticals (Durham, NC), is an analog of aspartic acid derived from *Streptomyces alanosinicus*. Alanosine's antitumor activity is based on its ability to interfere with the synthesis of adenosine, a molecule necessary for cellular growth and metabolism. There are two methods used by

cells to produce adenosine, either by *de novo* synthesis or by the "salvage pathway." Alanosine interferes with the *de novo* synthesis of adenosine in both malignant and normal cells. However, alanosine selectively deprives adenosine from certain cancer cells that lack the enzyme methylthioadenosine phosphorylase (MTAP), a required enzyme in the salvage pathway, without affecting normal cells of their only other means to make adenosine.

Alanosine was originally evaluated in phase I and phase II clinical trials by the National Cancer Institute (NCI) during the early 1980s but these trials were discontinued because alanosine did not produce significant response rates in common tumors such as breast or colon cancer, and caused toxicity typically associated with chemotherapy. Nevertheless, these dose-escalating studies have established Alanosine's dose-limiting toxicity (DLT).

Subsequently, investigators at the University of California, San Diego discovered that malignant cells from certain cancers lacked MTAP. This deficiency occurs in up to 30% of non-small cell lung cancer (nsclc) and 75% of primary brain tumors. Alanosine was active against MTAP-deficient tumors *in vitro*. Triangle is currently funding a phase II pilot efficacy studies with alanosine for the treatment of nsclc and brain malignancies that lack MTAP. A laboratory test is being developed to identify cancers that lack MTAP at tumor biopsy to select patients most likely to respond to therapy with alanosine.

Triangle has obtained an option from the Regents of the

Exhibit 1
Worldwide Incidence and Mortality of Prostate Cancer in 1998

Country	Incidence		Mortality	
	#	Rate[3]	#	Rate[3]
Denmark	3,857	148.4	742	28.6
France	34,775	122.1	6,501	22.8
Germany	48,350	117.1	9,767	23.7
Greece	3,193	61.0	652	12.5
Ireland	1,719	97.2	468	26.5
Italy	20,891	74.5	4,394	15.7
Luxembourg	217	104.2	55	26.6
Netherlands	8,192	105.7	2,062	26.6
Portugal	4,572	96.5	1,420	30.0
Spain	15,175	79.0	3,632	18.9
UK, England & Wales	24,569	85.5	4,914	17.1
UK, Scotland	1,977	79.5	395	15.9
EEC Total	167,486	98.2	35,003	20.5
Austria	4,600	117.4	949	24.2
Finland	2,277	91.0	641	25.6
Iceland	78	57.0	40	29.0
Malta	77	41.0	39	20.5
Norway	3,620	165.9	727	33.3
Sweden	7,648	172.9	1,319	29.8
Switzerland	5,785	161.6	1,128	31.5
Non-EEC	24,084	142.3	4,842	28.6
Bulgaria	2,054	48.5	516	12.2
Czech Republic	3,532	70.5	1,088	21.7
Hungary	4,249	89.8	1,093	23.1
Poland	8,372	44.5	2,769	14.7
Romania	3,691	35.4	833	8.0
Slovenia	389	41.1	194	20.6
Eastern Europe[1]	22,286	50.4	6,493	14.7
EUROPE[1]	213,856	92.3	46,338	20.0
Armenia	255	15.0	69	4.1
Belarus	1,345	27.4	472	9.6
Estonia	264	39.2	107	15.8
Kazakhstan	1,696	20.8	547	6.7
Kyrgyzstan	380	17.2	112	5.0
Latvia	417	37.1	155	13.8
Lithuania	678	39.6	300	17.5
Moldova	339	15.9	202	9.5
Russia	24,292	35.1	5,979	8.6
Tajikistan	498	16.7	72	2.4
Ukraine	7,876	33.5	1,919	8.2
Uzbekistan	1,576	13.3	198	1.7
Former USSR	39,616	30.4	10,132	7.8

— *continued on next page*

University of California that expires in September 1998 (with an option for Triangle to extend the exercise period for one year) for a worldwide license to use alanosine in treating various cancers lacking MTAP.

Hong Kong	340	10.4	43	1.3
Israel	1,194	43.4	339	12.3
Japan	17,179	27.9	3,105	5.0
Kuwait	194	16.4	49	4.1
Singapore	248	14.4	64	3.7
Thailand	1,410	4.8	352	1.2
Asia and Other	20,566	20.6	3,952	4.0
Argentina	10,535	59.6	2,581	14.6
Australia	8,549	93.0	2,319	25.2
Chile	2,925	40.8	1,351	18.9
Costa Rica	672	37.6	164	9.2
Cuba	5,798	105.2	1,422	25.8
New Zealand	2,207	124.0	467	26.3
Oceania, South America	30,685	71.2	8,304	19.3
Canada	14,850	103.5	4,100	28.6
USA	184,500	140.9	39,200	29.9
North America	199,350	137.2	43,300	29.8
Triad[2]	430,385	98.1	92,743	21.1

1 Excluding the Former USSR

*2 Triad includes North America, Japan and Europe**

3 Crude rate per 100,000 males

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; CA: A Cancer Journal For Clinicians, Cancer Statistics 1998:13

Diaziquone

Diaziquone (CI-904, NSC-182986, AZQ), under development by U.S. Bioscience, is a cytotoxic agent specifically designed to penetrate the BBB for the management of brain tumors. The company obtained an exclusive royalty-bearing license from the NCI to market AZQ in the USA but the term of exclusivity ended in March 1998. Although phase III clinical trials were completed in 1995, U.S. Bioscience has not pursued approval for this drug whose composition of matter patent expired in 1997 and the use patents expired in March, 1996. However, an IND is about to be filed to begin clinical trials anew in various cancer indications including brain cancer.

The CNS Cancer Consortium had conducted a phase III clinical trial in 1993 comparing diaziquone (AZQ) with carmustine (BiCNU, BCNU; Bristol-Myers Squibb) in adults with primary anaplastic glial brain tumors. Within three weeks of surgery, patients who underwent biopsy, subtotal resection, or gross total resection of an anaplastic glial brain tumor, were treated with whole brain radiotherapy (42-48 Gy), followed by a boost to the tumor bed of a total of 55-61 Gy. At 8 weeks following radiotherapy, patients were randomized to either treatment with daily intravenous AZQ (15 mg) for 3 days, every 4 weeks, or intravenous BCNU (200 mg), every 8 weeks. Chemotherapy continued for at least 1 year. Among the 249 randomized patients, neither AZQ nor BCNU was predictive of survival; 2-year survival was 22% and 25%, respectively (Halperin EC, etal, Am J Clinical Oncol, 1993 Aug, 16(4):277-83).

In another randomized phase III clinical trial also conducted in 1993, IV administration of AZQ and BCNU were compared in patients with cerebral anaplastic gliomas, 8 weeks following surgery and radiotherapy. Among patients who were older and diagnosed with GBM or gliosarcoma, MST was 37 weeks after randomization; among patients who were either older or diagnosed with GBM, MST was 61 weeks; in younger (<45) patients with anaplastic astrocytoma MST was 147 weeks. There was no significant difference in efficacy between AZQ and BCNU, but AZQ was better tolerated (Schold SC Jr, etal, J Clinical Oncology, 1993 Jan, 11(1):77-83).

Dibromodulcitol (DBD)

Dibromodulcitol (DBD; Mitolactol, Elobromol) is being developed by Biopharmaceutics (Bellport, NY) for the treatment of brain and cervical cancer. In 1996 Biopharmaceutics entered into a joint venture with Advanced Biological Systems (ABS) to commercialize DBD. According to the agreement, ABS will fund final product development and NDA filing, and will pay Biopharmaceutics $3.75 million, including $2.75 million in cash and stock and $1 million toward final product development and NDA filing. In return, Biopharmaceutics will provide 40% of its first $3.3 million in profits to ABS, and 45% thereafter.

In a phase II clinical trial conducted between March 1984 and January 1992, 42 children (mean age was 5 years and median age 3 years) with newly diagnosed progressive

low-grade gliomas (23 juvenile pilocytic astrocytomas, 11 astrocytomas, 1 oligodendroglioma,1 ganglioglioma, and 6 low-grade gliomas) were treated with a nitrosourea-based multiagent chemotherapy regimen consisting of procarbazine, thioguanine, and DBD administered before lomustine (CiCNU, CCNU; Bristol-Myers Squibb) and vincristine administered 1 and 3 weeks after CCNU. Patients were treated for six cycles or until disease progressed. Median time to treatment failure was 132 weeks; 8 patients died and the estimated 5-year survival rate was 78%. The treatment regimen was safe, easily delivered in an outpatient setting, and produced prolonged periods of disease stabilization in children with low-grade gliomas (Prados MD, etal, J Neurooncol 1997 May, 32(3):235-41). Oral DBD (500 mg/m^2) has been also evaluated in a small phase I/II clinical trial in Hungary in 5 children with brain cancer (Paal C, etal, Anti-Cancer Drugs, 1994 Oct, 5(5):539-47).

A randomized phase III trial of radiation therapy (RT) plus DBD versus RT plus BCNU in high-grade astrocytoma, was completed in June 1997. Survival and toxicity were observed in 238 patients with supratentorial Grade 3 and 4 astrocytoma. Patients were randomly assigned to RT (55-60 Gy) and, either oral DBD (200 mg/m^2) on days 1-10 every 5 weeks, or IV BCNU (200 mg/m^2), every 7 weeks. MST and median time to progression (TTP) were similar for all patients, at 41 weeks and 22 weeks in each arm, respectively. BCNU produced significantly greater hematologic and non-hematologic toxicities but no differences in treatment efficacy were observed (Elliott TE, etal, J Neurooncol, 1997 Jul, 33(3): 239-50).

Fluorodeoxyuridine (FdUrd)

FdUrd (5-fluoro2'-deoxyuridine) is a fluorinated pyrimidine that is cytotoxic to cells as a consequence of generation of 5-fluoro-2'-deoxyuridylate (FdUMP), a mechanism-based inhibitor of the enzyme thymidylate synthase (TS). FdUrd was developed by Taiho Pharmaceutical (Tokyo, Japan) in collaboration with Kagoshima University (Kagoshima, Japan) and Osaka University (Osaka, Japan).

FdUrd demonstrated minimal neurotoxicity *in vitro* and *in vivo*. Antitumor activity was observed against experimental tumor cells (mouse RSV-K glioma and 203 glioma and rat Walker 256 carcinoma) and human tumor cells (T98G and A-172 glioblastoma and Daoy medulloblastoma). In the 203 glioma model in mice, 250 mg of intrathecal FdUrd significantly extended survival time. Thymidine phosphorylase (TPase) activity was lower in normal and tumor tissue of the brain than that of in other organs, and neither TPase nor thymidine kinase (TK) were detected in CSF from most patients with malignant brain tumors including those with meningeal dissemination of malignancy. Data from this initial trial indicate that brain tissue and CSF are favorable sites for FdUrd chemotherapy, because the conversion rate of injected FdUrd to 5-FU would be minimal (Nakagawa H, etal, ASCO97, Abs. 1406:394a).

In a phase I/II clinical trial which began in Japan in January 1996, involving 13 patients (49-70 years; female=7, male=6; lung=7, colon=2, breast=1, brain=1, unknown=2) with neoplastic meningitis, 10 responded to intrathecal FdUrd (1-5 mg x 6-20 injections). There were no apparent serious side effects.

Hypericin

VIMRX Pharmaceutical (Wilmington, DE) is conducting an ongoing phase I/II clinical trial to evaluate the safety and efficacy of a chemically synthesized hypericin (VIMRxyn), a compound found naturally in plants of the *Hypericum* family, commonly known as Saint John's wort, in treating GBM. A formal analysis of the clinical data will be performed when 16 evaluable patients, i.e. those who have completed three months of treatment with VIMRxyn administered orally once daily, have been accrued. Twenty one patients have been enrolled in the study thus far. Treatment is extended beyond three months for responding patients. Contingent on the outcome of a formal analysis of all evaluable patients, VIMRX plans a phase II multicenter clinical trial to be initiated in mid-1998.

Mivobulin Isethionate

Mivobulin isethionate (CI-980, NSC 370147), in development by Parke-Davis for the treatment of a variety of solid tumors, is being also investigated in brain cancer. In an ongoing multicenter phase I/II clinical trial (protocol IDs: MDA-NCNSC-95003, NCI-T95-01010) being conducted under the auspices of the NCI, a total of 35 adults with malignant glioma are being treated with IV CI-980.

O(6)-benzylguanine

O(6)-benzylguanine (BG) is a suicide substrate inactivator for O(6)-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein that may be important in tumor resistance to alkylation chemotherapy. High levels of MGMT are found in human brain tumors. BG was able to reduce MGMT in human cells and in a mouse xenograft, to levels undetectable by antibody assay one hour post-treatment, therefore improving the efficacy of alkylating agents in cancer chemotherapy (Belanich M, etal, Cancer Chemother Pharmacol 1996 37:6 547-55).

A multicenter phase I clinical trial (protocol IDs: NABTC-9702, NCI-T96-0103) of BG as a presurgical (neoadjuvant) treatment in adult malignant glioma is ongoing at various sites spearheaded by the NCI and the American Brain Tumor Consortium. The study will enroll a minimum of 14 patients. Initiation of a phase II clinical trial in combination with BCNU, is imminent.

In March, 1998, Pacific Pharmaceuticals (San Diego, CA) obtained a worldwide exclusive license for BG, a series of related compounds and technologies which enhance the effectiveness of a class of currently used chemotherapeutic agents [O(6) alkylators]. These technologies are licensed to Pacific by Pennsylvania State University (State College, PA) on behalf of itself, the National Institutes of Health (NIH) and other universities. Terms of the agreement include royalties, license fees and milestone payments to be paid in cash or common stock of Pacific Pharmaceuticals.

Phenylacetate

Phenylacetate (NSC-3039, EL 530), a differentiation agent under development by Targon (Princeton, NJ), a joint venture between Elan Pharmaceuticals (Athlone, County Westmeath, Ireland) and Cytogen (Princeton, NJ), is in a phase II clinical trial (protocol IDs: NABTC-9402, NCI-T94-0087O, SWOG-9443), being conducted by the American Brain Tumor Consortium. The study is divided in two sessions. If ≥1 response is observed in the first 20 patients with recurrent adult malignant glioma and primitive neuroectodermal tumors, an additional 20 patients will be accrued over 5 months for Session I and 10 more for Session II.

Phenylbutyrate

Phenylbutyrate (NSC-657802, EL 532), a prodrug of phenylacetate, is also under development by Targon for treatment of various cancers including brain cancer. Phase I clinical trials, sponsored by the NCI, are ongoing. In one phase I clinical trial, being conducted at Johns Hopkins Oncology Center (protocol IDs: JHOC-NABTT-9605, NCI-T96-0086), up to 25 patients with refractory anaplastic astrocytoma or GBM, are being treated with oral phenylbutyrate *tid* until no longer effective; 4 patients are treated at each dose level to determine maximum tolerated dose (MTD). In a similar phase I clinical trial (protocol IDs: MSKCC-94111, NCI-T94-0170D) ongoing at Memorial Sloan-Kettering Cancer Center (New York, NY), 20-25 patients with refractory anaplastic astrocytoma or glioblastoma are being treated with oral phenylbutyrate *bid*.

Rebeccamycin Analog

Rebeccamycin analog (NSC 655649), originally developed by Bristol-Myers Squibb, is currently in phase I clinical trials for the indication of solid tumors in children and adults under primary funding by the NCI (NIH grant CA69853). Antitumor activity of rebeccamycin analog was determined in preclinical studies using human rhabdomyosarcoma, medulloblastoma, Ewing's sarcoma/PNET, and neuroblastoma cell lines; pediatric tumor explants; and the human tumor cloning assay. Tumor cells were exposed to various concentrations of rebeccamycin analog for 1 hour or continuously for 14 days. Twelve pediatric explant specimens were also exposed to rebeccamycin analog with significant activity observed in neuroblastoma and sarcomas. Results showed broad-spectrum activity against a variety of pediatric tumors *in vitro* at concentrations that have been achieved clinically during adult phase I clinical trials. In addition, compared to the 1-hour treatment, continuous exposure resulted in a 2-11 fold decrease in the IC_{50} of this agent (Weitman S, etal, AACR97, Abs. 4095:610).

A phase I dose escalation trial (protocol ID: POG-9670), being conducted at the University of Texas (San Antonio, TX), is assessing rebeccamycin analog at dose levels of 440 mg/m^2 to 760 mg/m^2, in pediatric patients with solid tumors. Twenty children diagnosed with solid tumors, including brain tumors, will be enrolled in the trial which is expected to conclude late in the summer of 1998.

Suramin

Suramin is under development by Parke-Davis for treatment of a variety of malignancies (see FO, p 310), including brain tumors. Suramin has completed phase III clinical trials for various indications. A phase II clinical trial (protocol IDs: EUC-DON-9420, NCI-T94-00330)

Exhibit 2
Age-specific Incidence of Prostate Cancer in Selected World Regions in 1998

	50-59		60-69		70-79		80+		>50	
World Region	**Incidence (#)**	**Rate***	**Incidence (#)**	**Rate***	**Incidence (#)**	**Rate***	**Incidence (#)**	**Rate***	**Incidence (#)**	**Rate***
Western Europe EEC	10,552	53.0	48,571	244.2	71,517	762.5	35,842	900.1	166,482	313.3
Western Europe non-EEC	1,517	77.5	6,984	356.6	10,284	1,041.5	5,154	1,240.1	23,940	450.0
Eastern Europe**	1,404	31.8	6,463	146.2	9,516	513.1	4,769	730.9	22,152	195.2
Total Europe**	13,473	51.3	62,018	236.1	91,317	747.2	45,765	906.2	212,574	304.5
Former USSR	2,496	19.6	11,489	90.4	16,916	496.3	8,478	688.0	39,378	131.1
Japan	1,082	13.0	4,982	59.9	7,335	236.8	3,676	296.3	17,076	81.4
United States	11,624	95.2	53,505	438.2	78,782	1,193.8	39,483	1,510.8	183,393	545.3
Total North America	12,559	91.9	57,812	423.2	85,122	1,166.4	42,661	1,477.4	198,154	528.3
Triad (North America, Japan and Europe)**	27,114	56.2	124,812	258.7	183,775	812.6	92,103	1,003.4	427,804	333.5

**Number of men over age 50 years with prostate cancer per 100,000 within age groups*
***Excluding the Former USSR*

Exhibit 3
Estimated Age-specific Prevalence of Latent Prostate Cancer in Selected World Regions in 1998

World Region	50-59	60-69	70-79	80+	> 50 years	All Ages
	#	#	#	#	#	Rate*
Western Europe EEC	4,396,142	7,181,028	3,545,411	2,138,390	17,260,970	324.8
Western Europe non-EEC	432,842	707,040	373,234	223,192	1,736,309	326.4
Eastern Europe**	977,041	1,595,981	701,064	350,424	3,624,511	319.4
Total Europe**	5,806,025	9,484,049	4,619,710	2,712,006	22,621,790	324.0
Former USSR	2,807,169	4,585,466	1,288,508	661,719	9,342,862	311.0
Japan	1,837,226	3,001,079	1,170,960	666,372	6,675,638	318.4
United States	2,698,451	4,407,877	2,494,515	1,403,402	11,004,246	327.2
Total North America	3,018,994	4,931,480	2,758,574	1,550,645	12,259,692	326.9
Triad (North America, Japan and Europe)**	10,662,245	17,416,609	8,549,243	4,929,023	41,557,120	323.9

**Number of existing cases of prostate cancer per 1,000 men*
***Excluding the Former USSR*
Note: Prevalence is calculated by age group as follows: 50-59 (22.1%), 60-69 (36.1%), 70-79 (37.8%), 80+ (53.7%)

involving 25 patients with adult recurrent or progressive malignant glioma is ongoing at Emory University (Atlanta, GA).

One of the major side effects of the drug is sensorimotor polyneuropathy which may be attributed, in part, to the fact that suramin prevents insulin-like growth factor (IGF)-II and other growth factors from activating their receptors. IGF-I and IGF-II have high affinity receptors in the brain capillary. Suramin prevented IGF-II-stimulated IGF-I receptor (IGF-Ir) tyrosine phosphorylation as was demonstrated by adding suramin (50-400 mg/ml) to SH-SY5Y human neuroblastoma cells, in an *in vitro* model of neuronal growth and differentiation (Sullivan KA, etal, Brain Res, 1997 Jan 9, 744(2): 199-206).

Temozolomide

Temozolomide, under development by Schering-Plough (Madison, NJ), is an imidazotetrazine analog that has shown a broad spectrum of antineoplastic activity in preclinical studies. Temozolomide is a prodrug of mitozolomide. A phase I clinical trial of temozolomide in children and adolescents (ages 1-21) with recurrent solid tumors has been completed. Temozolomide treatment stratification was dependent upon previous craniospinal irradiation (CSI) therapy. Temozolomide was administered orally daily, for 5 days, with subsequent courses administered every 21-28 days, after full hematologic recovery. In the 25 evaluable patients in the non-CSI group, DLT did not occur during the first three daily dose levels (100, 150 and 180 mg/m^2) but did occur at 215 mg/m^2 in one of 6 patients, presenting as non-dose limiting Grade 3 thrombocytopenia and neutropenia. In 22 evaluable CSI patients, DLT occurred in 3 of 8 patients at the 245-260 mg/m^2 daily dose, in one of 6 patients at the 100 mg/m^2 dose, in one of 9 patients at the 180 mg/m^2 dose, and in 2 of 4 patients at the 215 mg/m^2 dose. DLT included thrombocytopenia and neutropenia and 56% of patients experienced Grade 3 or less nausea and vomiting. No non-hematologic DLT occurred. After two cycles of temozolomide, disease stabilized in 10 patients, and 3 experienced PR; one with a supratentorial primitive neuroectodermal tumor subsequently had a CR. A phase II clinical trial of temozolomide is ongoing in children with recurrent brain tumors using a daily dose of 21.5 mg/m^2 for those without prior CSI and 180 mg/m^2 for those with prior CSI, for five days in 28-day cycles (Nicholson S, etal, ASCO97, Abs. 751:214).

In a phase II multicenter clinical trial, oral temozolomide monotherapy is being evaluated in comparison to procarbazine (protocol IDs: SPRI-C94-091, NCI-V95-0651); 200 patients are expected to be enrolled in each arm.

Schering-Plough submitted a centralized marketing authorization application (MAA) to the European Union's European Medicines Evaluation Agency (EMEA) on January 12, 1998, seeking clearance of temozolomide for treatment of patients with recurrent malignant gliomas (GBM and anaplastic astrocytoma). Schering-Plough has exclusive worldwide rights to market temozolomide through a licensing agreement with Cancer Research Campaign Technology (London, UK).

UCN-01

UCN-01, a staurosporine analog originally discovered by the NCI, is currently under development by Kyowa Hakko Kogyo (Tokyo, Japan). UCN-01 is a protein kinase C (PKC) inhibitor that may block G2 arrest of the cell cycle following DNA damage. It also acts on cell cycle-dependent

mechanisms, such as induction of expression of p21 protein, and inhibition of cyclin-dependent Rb kinases. In animal and *in vitro* studies UCN-01 was shown to be a potent inhibitor of malignant glioma cell proliferation, and also exhibited cytostatic and cytotoxic effects in *in vitro* inhibition-recovery studies of clonogenic activity. Although proliferation resumed after short-term (6- and 24-hour) exposures to UCN-01, recovery of proliferative activity in longer exposures was severely compromised. When used in conjunction with chemotherapeutic agents, UCN-01 enhanced inhibition of glioma cell proliferation, exhibited synergistic effects with cisplatin, and additive effects with 1,3-bis(2-chloroethyl)-1-nitrosourea. In *in vivo* studies, administration of UCN-01 by continuous intraperitoneal infusion in nude rat models, elicited significant activity against U-87 glioma xenografts at dose levels that were well tolerated (Pollack IF, etal, Journal of Neurosurgery, 1996 Jun, 84(6):1024-32).

Exhibit 4
Incidence Trends of Prostate Cancer in the USA

Year	Incidence		Change in Incidence	
	(#)	Rate$^{\gamma}$	Rate$^{\gamma}$	PSA tests per 100,000 men
1994-1998			-3.1	
1998	184,500	140.9	-115.4	
1997	334,500	256.3	12.1	
1996	317,000	244.2	-2.5	
1995	315,776	246.7	102.7	
1992-1994*			-46.1	
1994	183,256	144.0	-46.1	
1992	236,695	190.1	22.8	
1989-1992**			77.7	18,000
1991	203,437	167.3	35.3	
1990	160,512	132.0	19.6	
1989	136,678	112.4	6.6	
1976-1988			32.3	1,430
1988	128,653	105.8	3.0	
1987	125,005	102.8	11.8	
1986	110,656	91.0	3.0	
1985	107,008	88.0		
1976	89,376	73.5		

** The incidence rate of whites fell from 1992 to 1994 and blacks fell 1 year later*
*** Initial screenings detect latent + recent cancers, inflating incidence rates*
$^{\gamma}$ Number of prostate cancer cases per 100,000 males
Source: Potosky AL, etal, Journal of the American Medical Association, Feb 15, 1995; 273(7):549-552

A phase I clinical trial of UCN-01 (NCI-95-C-0171G, NCI-T95-0052N) in 29 patients with refractory solid tumors or lymphoma is ongoing at the NCI. Patients are treated with UCN-01 by IV infusion continuously for 3 days during the first week, then continuously for 2 days every 4 weeks, for as long as benefit is shown.

RECEPTOR TARGETING STRATEGIES

CEP751

CEP751, under development by Cephalon (West Chester, PA), is an analog of K252a that relatively specifically inhibits neurotrophin tyrosine kinase receptors trkA, trkB and trkC. Favorable neuroblastomas (NBL) express trkA and trkC while unfavorable NBL primarily express trkB. Also, both trkB and trkC can be expressed by medulloblastomas (MBL). *In vitro*, CEP751 inhibited cell growth of both NBL and MBL cell lines examined and, *in vivo*, CEP751 inhibited the growth of two different NBL cell lines. No evidence of toxicity was observed (Evans AE, etal, ASCO97, Abs. 1878:522). CEP-751 has no effect on activity of receptors for EGF, IGF-I, insulin or on erbB2 and, although inhibition of receptors for PDGF and basic FGF was observed, it occurred with lesser potency than inhibition of trk (Camoratto AM, etal, Int J Cancer, 1997 Aug 7, 72:4673-9).

IL4 (38-37)-PE38KDEL

Interleukin-4 (IL4) (38-37)-PE38KDEL, patented by three NCI physicians, is being developed by the agency for treatment of brain tumors. IL-4 receptors were detected by reverse transcriptase (RT) PCR in 16 of 21 surgical samples of high-grade astrocytoma and glioblastoma, but not in normal brain tissues. Also, human malignant astrocytoma cell lines expressed a high-affinity to IL-4r. IL4 (38-37)-PE38KDEL, a chimeric protein consisting of IL-4 and a truncated form of Pseudomonas exotoxin A, was highly cytotoxic to IL-4R-bearing glioblastoma cells. Intrathecal administration of 2- and 6-mg/kg dose in monkeys achieved high cerebrospinal fluid levels, which may have significant cytotoxic activity against malignant astrocytoma without any CNS or other abnormalities (Puri RK, etal al, Cancer Res 1996 Dec 15 56:24 5631-7). This immunotoxin is currently a phase I/II clinical trial (protocol IDs: JWCI-BB-IND-7004, NCI-V97-1281) being conducted at John Wayne Cancer Institute (Santa Monica,

CA) in adult recurrent malignant astrocytoma. The study is testing this agent by separating enrollees in two groups, those with superficial astrocytomas (Group A) and those with relatively inaccessible tumors (Group A). A maximum of 24 patients will be accrued, 12 within each group, and treated by dose escalation to MDT.

IL13-PE38QQR

IL13-PE38QQR, is a fusion protein combining interleukin 13 (IL-13) with Pseudomonas exotoxin. A range of brain cancer cells are covered by receptor sites which accept interleukin 13. This fusion toxin selectively targets and kills such cancer cells in the brain. Pennsylvania State College of Medicine (Hershey, PA), in collaboration with the NIH, has licensed this anticancer fusion toxin to NeoPharm (Lake Forest, IL).

SU101

SU101, a small synthetic molecule that inhibits the platelet-derived growth factor (PDGF) tyrosine kinase (TK) signaling pathway and is structurally similar to leflunomide, under development by Sugen (Redwood City, CA), entered a pivotal phase III clinical trial in January 1998, in GBM patients in first relapse. An estimated 380 patients in over twenty sites in the USA and Canada will participate in this clinical trail which will compare the efficacy of single-agent SU101 against that of single-agent procarbazine. Patients are being randomized to either a 4-day loading dose (440 mg/m^2) of SU101, to be followed by weekly administration, or oral procarbazine (150 mg/m^2) administered in 28-day cycles. The primary endpoint is a more than 40% increase in survival, while secondary endpoints include time to progression, objective response rate, and quality of life. An interim analysis is anticipated in mid-1999.

Several other trials of SU101 in brain cancer are ongoing. Among them are a phase II clinical trial of SU101 in combination with BCNU for first-line treatment of newly-diagnosed GBM and a 24-patient phase I clinical trial in pediatric refractory CNS malignancies. In this latter trial, sponsored by the NCI (protocol IDs: NCI-97-C-0087), SU101 dose escalation consists of 5 dosage levels to MTD, delivered as a 96-hour continuous IV, on days 1-4, in a 21 day treatment cycle. Also see FO, pp 195 and 102.

THERAPY ENHANCEMENT

Various techniques are being developed to sensitize tumor cells to chemotherapy and/or radiation therapy (see FO, pp 707-709). One such approach, modulation of tumor perfusion, represents an attractive option. Improving tumor oxygenation and perfusion using carbogen inhalation and nicotinamide or vasoactive agents (flunarizine, verapamil, nicotinamide) enhances the effects of radiotherapy and improves delivery of chemotherapeutic agents to the tumor. Research is currently in progress into the efficacy of accelerated radiotherapy in combination with carbogen inhalation and administration of nicotinamide in tumors of the head and neck, bladder, bronchi and brain (Bernsen HJ, etal, Nederlands Tijdschrift voor Geneeskunde, 1997 Feb 22, 141(8):364-8).

Exhibit 5
Mortality Trends of Prostate Cancer in the USA

Year	Deaths	Rate*
1998	39,200	29.9
1997	41,800	32.0
1996	41,400	31.9
1995	41,400	32.2
1994	33,088	26.0
1992	33,244	26.7
1990	32,832	27.0
1989	33,562	27.6
1985	28,220	23.4
1976	26,432	22.1

**Number of deaths per 100,000 males*

Source: Potosky AL, etal, Journal of the American Medical Association, Feb 15, 1995; 273(7):549-552

Radiosensitization

RSR-13, 2-[4-[[(3,5-dimethylanilino)-carbonyl]-methyl]phenoxy]-2-methylpropionic acid, under development by Allos Therapeutics (Denver, CO), is a synthetic hemoglobin allosteric modifier that increases oxygen delivery through allosteric modification of the hemoglobin molecule, resulting in a shift in the hemoglobin/oxygen dissociation curve in favor of oxygen delivery.

A phase II clinical trial (protocol ID: JHOC-NABTT-9707) in newly-diagnosed adult GBM is ongoing. A completed 36-patient phase Ib clinical trial (protocol IDs: JHOC-NABTT-9606, NCI-T96-0085) evaluated safety and tolerance of repetitive daily intravenous administration of RSR-13 in one group, and every other day dose frequency in another. The drug was administered over 60 minutes by continuous infusion via a central venous access device.

Chemosensitization

Artificial oxygen carriers may enhance the effectiveness of certain chemotherapeutics used in the treatment of brain cancer. A multicenter phase I/II clinical trial, involving 99 patients with malignant gliomas with radiographic progression after definitive surgery and radiotherapy, evaluated toxicity and response rate following BCNU combined with oxygen inhalation and escalating doses of fluosol. All patients were treated with a fixed dose (200 mg/m^2) of BCNU along with 100% oxygen and escalating doses (150, 275, 400 and 600 ml/m^2) of the perfluorochemical fluosol, repeated every 6 weeks for a maximum of 6 cycles. Treatment was well tolerated but dose reductions were required at least once in 18 patients and a treatment delay was necessary at least once in 33 patients. Grade 3-4

leukopenia occurred in 6 patients (12 events), Grade 3-4 thrombocytopenia in 10 patients (25 events) and Grade 3-4 liver enzyme elevations in 18 patients (31 events). Higher fluosol doses did not produce either increases in toxicity or responses. Response or stabilization was seen in 57% of patients (38% of these represented stabilized disease). Median time to progression was 45 weeks, and MST of responders was 66 weeks. Response/stabilization was seen in 45% of those with GBM, lasting a mean period of 24 weeks, and 68% of those with with anaplastic astrocytomas, lasting 50 weeks. Future studies will be performed using fluosol at the dose of 400 ml/m^2 (Hochberg F, etal, Journal of Neurooncology, 1997 Mar, 32(1):45-55).

Chemoprotection

Dexrazoxane (ICRF-187, Zinecard; Pharmacia & Upjohn), which was demonstrated to rescue healthy mice from lethal doses of topoisomerase II poisons, is a promising lead compound for the development of schedules using high-dose topoisomerase II poisons in the treatment of brain tumors and metastases. In mice the ICRF-187 lethality (LD10) was 500 mg/kg. Within a wide non-toxic dose range (50-250 mg/kg), ICRF-187 protected against amsacrine (m-AMSA) and etoposide lethality. When administered in combination with ICRF-187, LD10 of etoposide increased from 34 mg/kg for the single agent to 122 mg/kg, corresponding to a 3.6-fold etoposide dose escalation. In contrast, ICRF-187 did not protect against lethal doses of the non-topoisomerase II-directed drug paclitaxel. Because the hydrophilic ICRF-187 is not expected to cross the blood-brain barrier, in contrast to the lipophilic etoposide, the effect of this drug combination was studied in mice inoculated intracranially with L1210 cells. A significant increase in life span was observed in mice treated with the combination as compared to an equitoxic dose of etoposide alone. Therefore, ICRF-187 is a powerful nontoxic protector against the lethality of the topoisomerase II-directed drugs etoposide and m-AMSA *in vivo* and the brain tumor model demonstrates the superiority of high-dose etoposide treatment with ICRF-187 protection. This implies that higher doses of cytotoxic drugs against brain tumors may be delivered while simultaneous administration of ICRF-187 would protect normal tissues (Holm B, etal, Cancer Chemotherapy and Pharmacology, 1996, 38(3):203-9).

NOVEL APPROACHES TO PREVENT/ TREAT METASTASES

While distant metastases are rare in patients with primary brain malignancies, regional infiltration is common and is responsible for failure of local therapies, resulting in tumor recurrence, progression and death. Preventing local metastasis of brain tumors is vital in improving treatment efficacy and extending survival. Techniques used to cut off the ability of tumors to spread include inhibition of neoangiogenesis by blocking endothelial proliferation and migration; selectively targeting tumor blood vessels by exploiting unique markers; prevention of proteolytic degeneration of the extracellular matrix by products of the tumor; or interfering with a number of other means via which tumors spread, which are coming to light as research continues in this still poorly understood area.

Exhibit 6
Incidence and Mortality Rates of Prostate Cancer in the USA by Race and Ethnicity

Race/Ethnicity	Incidence Rate*	Mortality Rate*
African American	180.6	53.7
White	134.7	24.1
Hispanic	89.0	15.3
Japanese	88.0	11.7
Filipino	69.8	13.5
Hawaiian	57.2	19.9
American Indian	52.5	16.2
Alaska Native	46.1	<10.0
Chinese	46.0	<5.0
Vietnamese	40.0	–-
Korean	24.2	–-

** Age-adjusted incidence and mortality rate per 100,000 population (adjusted to the 1970 USA standard population)*

Source: NCI Surveillance, Epidemiology, and End Results Program (SEER), 1996 in CA:A Cancer Journal For Clinicians 1998; 48(1):38

Matrix Metalloproteinase (MMP) Inhibitors

Matrix metalloproteinases (MMPs), a family of at least fifteen secreted and membrane-bound zinc-endopeptidases, are considered essential for the processes of angiogenesis and metastasis in malignacy. Control/inhibition of MMP activity is, therefore, a goal of various drug development strategies. Tissue inhibitors of metalloproteinases (TIMPs) are naturally occurring proteins that specifically inhibit matrix metalloproteinases that maintain balance between matrix destruction and formation. An imbalance between MMPs and associated TIMPs may play a significant role in the invasive phenotype of malignant tumors. TIMP-1 has been shown to inhibit tumor-induced angiogenesis in experimental systems (Wojtowicz-Praga SM, etal, Invest New Drugs 1997 15:1 61-75).

The production and activation of pro-gelatinase A (progel A) by a novel membrane-type matrix metalloproteinase-1 (MT-MMP-1) in tumor tissues may play a crucial role for the invasion and metastatic processing in CNS cancer. Expression of MT-MMP-1 on neuroblastoma cells is associated with advanced stage and a poor prognosis. Therefore, MT-MMP-1 may be an important prognostic determinant in pediatric CNS tumors (Masae Sakakibara, etal, ASCO97, Abs 1876:521).

Bryostatin-1, an antineoplastic agent being developed by Bristol-Myers Squibb, is a macrocyclic natural lactone isolated from the marine bryozoan, *Bugula neritina*. In culture, bryostatin-1 has been shown to induce differenti-

Exhibit 7
Drugs in Development for Treatment of CNS Cancer

Developer ❑ Affiliates	Generic Name ❑ Numeric Designation ❑ Brand Name	Description ❑ Administration Route	Status ❑ Indications
Allos Therapeutics ❑ NCI	2-[4-[[(3,5-dimethylanilino)-carbonyl]-methyl]phenoxy]-2-methylpropionic acid ❑ RSR-13	Synthetic hemoglobin allosteric modifier; increases oxygen delivery through allosteric modification of the hemoglobin molecule, resulting in a shift in the hemoglobin/oxygen dissociation curve in favor of oxygen delivery ❑ infusion via central venous access	Phase II (o3/98)➢USA ❑ adult glioblastoma multiforme (GBM)
Alkermes ❑ Alza/Alkermes Clinical Partners	Receptor-mediated permeabilizer-7 (RMP-7) ❑ Cereport	RMP-7 is a nine amino acid peptide based on bradykinin that temporarily increases the permeability of the blood-brain barrier; in combination with carboplatin ❑ intra-arterial, intravenous (IV)	Phase III (b2/98)➢USA ❑ primary glioma; phase I/II (b8/96)➢USA ❑ brain cancer, pediatric; phase II (o10/97)➢USA ❑ brain cancer, adult, recurrent; phase II (b2/98)➢USA ❑ brain cancer (intra-arterial)
Avigen ❑ U California San Francisco, Nagoya U	Adeno-associated virus (AAV) vectors	Gene transfer of DNA to specific tissues or disease sites using AAV vectors to sensitize cells to chemotherapy; may deliver and achieve simultaneous expression of the tk gene and an immunostimulatory lymphokine gene in tumor cells	Preclin (9/97)➢USA ❑ brain cancer, GBM
Bavarian Nordic Research Institute ❑ Institute of Virology, GSF-Forschungszentrum für Umwelt und Gesundheit	Promoter conversion vectors	Brain specific (astrocyte) promoters are introduced to allow gene expression only in targeted cell types ❑ injection	Preclin (1/98)➢Europe
Biogen	Interferon (IFN) β-1a ❑ Avonex	Cytokine; protein derived from fibroblasts	Phase II (5/97)➢USA ❑ glioma (see FO, p 725)
Biopharmaceutics ❑ ABS Group, Chinoin, NCI	Dibromodulcitol (DBD) ❑ Mitolactol, Elobromol	An alpha omega substituted hexitol; stereoisomer of dibromomonnitol ❑ PO	Phase III (9/96)➢USA, Europe ❑ brain cancer; phase II (c92)➢USA ❑ pediatric newly-diagnosed progressive low-grade gliomas
Briana Bio-Tech ❑ U Alberta		Immunogene therapy; autologous tumor cells transfected with GM-CSF and B7-2 genes using a viral vector delivery system	Preclin (3/98)➢Canada ❑ GBM
Bristol-Myers Squibb ❑ NCI, Imperial Cancer Research Technology (ICRT) (lincesor)	Bryostatin-1	Natural macrocyclic lactone derived from marine bryozoan *Bugula neritina*; ligand and modulator of protein kinase C (PKC) ❑ IV	Phase II (o12/97)➢USA ❑ adult high-grade recurrent astrocytoma, mixed gliomas
British Biotech ❑ Tanabe Seiyaku (licensee, Japan)	Marimastat ❑ BB-2516	Matrix metalloproteinase inhibitor (MMPI); inhibits metalloproteases by chelating Zn at the active site ❑ PO	Phase III (3/97)➢UK, USA ❑ GBM and gliosarcoma (second-line therapy with gamma knife radiosurgery), also see FO, pp 194 and 310
Canji (Schering-Plough)	ACN-p53 TSG	Adenovirus-mediated replacement of defective p53 with wild-type version ❑ intratumoral, bolus infusion	Phase I (o2/98)➢USA ❑ solid tumors
Cephalon ❑ Children's Hospital of Philadelphia	CEP-751	Analog of K252a that blocks Trk receptors, thus inhibiting growth of neuroblastoma cell lines *in vitro* and *in vivo*	Preclin (2/98)➢USA ❑ brain cancer, neuroblastoma, medulloblastoma

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Chiron ❑ Ligand Pharmaceuticals (Canadian rights)	Aldesleukin ❑ NSC-373364 ❑ Proleukin	Recombinant IL-2; stimulates lymphokine-activating killer (LAK) cells, natural killer (NK) cells and production of cytokines such as IFN-γ ❑ injection	Phase I/II (o2/98)➢USA (NCI, U Colorado Cancer Center) ❑ advanced neuroblastoma and recurrent primary brain tumors (protocol IDs: UCHSC-COMIRB-93426, NCI-T94-00650)
Chiron ❑ Novartis and Rhône-Poulenc Rorer (licensees)		Retrovirally-mediated incorporation into tumors of the herpes simplex virus-thymidine kinase (HSV-tk) gene with subsequent treatment with ganciclovir ❑ intratumoral stereotactic injection	Phase I (o2/98)➢USA ❑ adult recurrent malignant glioma (MGH-H97-1122, NCI-H97-1122)
Duke U Medical Center ❑ NIH	^{131}I-labeled anti-tenascin chimeric MAb 81C6	Following iodination (^{131}I-label), MAb 81C6 was shown to efficiently localize and destroy human glioma ❑ intracranial	Phase II (o3/98)➢USA ❑ primary or metastatic anaplastic glioma (protocol IDs: DUMC-221-96-2R3, NCI-H96-0009)
EntreMed ❑ Children's Hospital at Harvard Medical School (licensor), NCI	Thalidomide and its chemical analogs	Anti-angiogenesis compound; may block bFGF and VEGF ❑ PO	Phase II (b3/96)➢USA ❑ GBM, anaplastic astrocytoma (orphan drug)
Ergo Science ❑ The Rowland Institute	Benzophenothiazine analogs ❑ ER-470 (EtNBS) and ER-480	Photochemotherapeutic dyes ❑ injection	Preclin (4/97)➢USA
Genetic Therapy (Novartis)	GLI 328	Gene transfer by retrovirus HS-tk suicide gene ❑ intratumoral	Phase I/II (b7/95; c97); phase II (o2/98)➢USA; phase III (o2/98) ➢Europe ❑ brain cancer, glioma
Genetronics	Electroporation therapy (EPT) ❑ MedPulser	After genes are injected into the tumor, a very short, pulsed rotating electric field is applied to the tumor by means of insertion of a special array of needles and use of an optimized combination of voltage and pulse duration ❑ intralesional	Preclin (1/98)➢USA (see FO p)
Guilford Pharmaceuticals ❑ Rhône-Poulenc Rorer, Orion	Carmustine wafer ❑ Gliadel (20% BCNU)	Drug delivery system consisting of a biodegradable polymer that contains carmustine (BCNU) ❑ perioperative	Phase III (4/97)➢USA ❑ brain cancer, malignant glioma (see FO, pp 710-711)
IDEC Pharmaceuticals	9-aminocamptothecin ❑ NSC-603071, 9-AC	Water soluble camptothecin analog; small molecule; topoisomerase I inhibitor ❑ intravenous (IV)	Phase II➢USA (NCI, Cleveland Clinic) ❑ adult GBM (protocol IDs: CCF-IRB-1104, NCI-T94-0166D)
Ilex Oncology ❑ Sanofi (licensor), Jenssen Pharmaceutica (licensee)	Crisnatol mesylate	Polycyclic aromatic hydrocarbon ❑ continuous IV	Phase III (discontinued 6/97)➢ USA ❑ adult GBM; phase I (c97; discontinued 6/97)➢USA ❑ pediatric gliomas
Ilex Oncology	Alpha difluoromethylornithine HCl (DFMO) ❑ Ornidyl	Antiparasitic ❑ injection, PO	Phase III (1/96)➢USA ❑ brain cancer
Immune Response ❑ Sidney Kimmel Cancer Center		Irradiated patient's glioblastoma cells genetically modified with an antisense gene to inhibit transforming growth factor β (TGF-β) production are injected directly under the skin to stimulate an immune response ❑ *ex vivo*; injection	Phase I (b12/96)➢USA ❑ brain cancer
IntroGene		HSV-tk gene therapy using a novel adenoviral-vector-producing cell line, PER-C6, to package the gene for delivery	Phase I (o2/98)➢Europe ❑ glioma (IGN-HSVtk-GL-06) and leptomeningeal metastases (IGN-HSVtk-LM-06)

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John Hopkins U	2-[4-[[(3,5-dimethylanilino)-carbonyl]-methyl]phenoxy]-2-methylpropionic acid ❑ RSR-13	Oxygen delivery agent ❑ continuous infusion via a central venous access device	Phase Ib➢USA ❑ GBM treated by cranial irradiation (protocol IDs: JHOC-NABTT-9606, NCI-T96-0085)
Kyowa Hakko Kogyo ❑ NCI	UCN-01	Staurosporine analog; protein kinase C (PKC) inhibitor that may block G2 arrest of the cell cycle following DNA damage; also acts on cell cycle-dependent mechanisms, such as induction of expression of p21 protein, and inhibition of cyclin-dependent Rb kinases ❑ intravenous (IV)	Phase I (o8/97)➢USA ❑ solid tumors
Lexigen (was Fuji ImmunoPharmaceuticals) ❑ Scripps Research Institute		Chimeric anti-GD2 (MAb ch14.18) ❑ intravenous (IV)	Phase III (o2/98)➢Europe; phase II (c97)➢USA ❑ pediatric recurrent or refractory neuroblastoma
Magainin Pharmaceuticals	Squalamine	Cationic steroid characterized by a condensation of an anionic bile salt intermediate with the polyamine, spermidine; aminosterol; dogfish shark-derived peptide ❑ intravenous (IV)	IND (f8/97)➢USA ❑ solid tumors
Medarex ❑ Dartmouth Medical, Merck KGaA	MDX-447 ❑ EMD 82633	Bispecific therapeutic consisting of a Trigger MAb fragment and a targeting EGFr component provided by Merck KGaA; constructed by crosslinking F(ab') fragments of MAb H22 to FcgRI and MAb H425 to EGFr ❑ injection	Phase I/II (b9/95, c7/97)➢USA ❑ cancers that overexpress EGFr
Medarex ❑ Dartmouth Medical, U Vaudrois	MDX-260	Bispecific therapeutic consisting of a Trigger component and a component targeting GD-2 antigen	Preclin (3/97)➢USA ❑ solid tumors
Miravant Medical Technologies ❑ Pharmacia & Upjohn	SnET2 ❑ Purlytin	Photodynamic therapy using tin ethyl etiopurpurin (SnET2), which, when exposed to appropriate light wavelength, acts as a catalyst to generate a highly reactive form of oxygen which destroys the membrane of the cells containing the drug ❑ intravenous (IV)	Preclin (2/98)➢USA ❑ brain cancer
Roberts Pharmaceuticals ❑ NCI (licensor), Nycomed Pharma	Etanidazole ❑ NSC-301467, SR-2508, EF5	Nitroimidazole; hypoxic cell sensitizer ❑ intravenous (IV)	Phase Ib (10/96)➢USA ❑ brain cancer (see FO, p 707)
National Cancer Institute (NCI)	Carboxy-amido-triazole (CAI) ❑ NSC-609974	Synthetic signal transduction inhibitor that modulates non-voltage-gated calcium influx-regulated (non-excitable) signal pathways; metastasis inhibitor that targets a pertussin toxin-sensitive G protein; reversibly inhibits angiogenesis, tumor cell proliferation, and metastatic potential ❑ PO	Phase I (o2/98)➢USA ❑ malignant glioma
National Cancer Institute (NCI)	Transferrin-CRM107	Compound consisting of transferrin linked to diphtheria toxin ❑ intratumoral using a pressurized pump	Phase I (o2/98)➢USA
National Cancer Institute (NCI)	Rebeccamycin analog	Antibiotic ❑ infusion	Phase I (3/98)➢USA ❑ pediatric brain tumors (protocol ID: POG-9670)

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National Cancer Institute (NCI)	IL4 (38-37)-PE38KDEL	Genetically altered interleukin-4 (IL-4) linked to Pseudomonas exotoxin A ❑ intrathecal	Phase I/II (o3/98)➢USA ❑ brain cancer
NeoPharm ❑ NCI, BioChem Therapeutics	Broxuridine (BUdR) ❑ Broxine	BUdR, an analog of thymidine, is incorporated into the DNA of tumor cells where it replaces significant amounts of thymidine, rendering tumor cells more sensitive to radiation ❑ infusion	Phase III (4/96)➢USA; NDA (f4/97) ❑ primary brain cancer, astrocytomas (see FO, p 707)
NeoPharm ❑ NIH, Pennsylvania State College of Medicine	hIL13-PE38QQR	Combination of interleukin 13 (IL-13) and Pseudomonas exotoxin	Research (2/98)➢USA ❑ brain cancer
Neurobiological Technologies	Corticotropin - releasing factor (CRF) ❑ Xerecept	A synthetic preparation of the endogenous peptide hormone, CRF ❑ continuous or intermittent IV infusion	Phase II (6/97)➢USA ❑ edema associated with brain cancer (see FO p 725)
Novartis	CGP 57148	2-phenylaminopyrimidine; protein tyrosine kinase (PTK) inhibitor; selectively kills p210BCR-ABL-expressing cells and inhibits other activated ABL tyrosine kinases (p185BCR-ABL and TEL-ABL) and TEL-PDGFR (platelet-derived growth factor receptor)	Preclin (7/97)➢USA ❑ glioma
Novopharm Biotech	GLIOMAb-H	Human MAb; targets cancer cells that are both resting and actively dividing	Phase I (b1/96)➢USA ❑ glioma, neuroblastoma
OncoTech/Phoenix Pharmaceuticals	L-buthionine sulfoximine (BSO)	Reduces intracellular glutathione (GSH) and increases cytotoxicity of melphalan (L-PAM) *in vitro*	Phase I (5/96)➢USA ❑ neuroblastoma
OXiGENE	Neu-Sensamide	A neutralized formulation of metoclopramide ❑ intramuscular	Phase I/II (b8/96)➢Europe ❑ brain cancer (see FO, p 709)
Pacific Pharmaceuticals ❑ Binary Therapeutics, U California, San Francisco	Boronated porphyrin compound (BOPP)	Photosensitizer	Preclin (1/98) USA ❑ metastatic brain cancer, refractory malignant glioma (see FO, p 709)
Pacific Pharmaceuticals ❑ Pennsylvania State U	O(6)-benzylguanine (BG)	O(6) BG is a suicide substrate inactivator for O(6)-methyl-guanine-DNA methyltransferase (MGMT), a DNA repair protein found in high levels in brain tumors ❑ infusion	Phase I➢USA ❑ adult malignant glioma (protocol IDs: NABTC-9702, NCI-T96-0103)
Parke-Davis ❑ NCI	CI-958, NSC-635371	Benzothiopyranoindazole; DNA intercalator ❑ infusion	Phase I➢USA ❑ recurrent pediatric neuroblastoma
Parke-Davis	Mivobulin isethionate ❑ CI-980, NSC 370147	Synthetic mitotic inhibitor that binds to the colchinine-binding site on tubulin which is distinct from the binding site of the vinca alkaloids ❑ infusion	Phase I/II (b7/96)➢USA (#T95-0101) ❑ malignant, recurrent, progressive glioma, phase II (b8/96)➢USA (#T96-0027) ❑ newly-diagnosed, malignant glioma
Parke-Davis ❑ NCI (CRADA)	Suramin ❑ NSC-34936 ❑ Moranyl	Polysulfonated napthylamine; non-specific cell killing agent; inhibits angiogenesis and enhances apoptosis ❑ infusion	Phase II (02/98)➢NCI (Emory U) ❑ adult recurrent or progressive malignant glioma (protocol IDs: EUC-DON-9420, NCI-T94-00330); also FO p 310
Pharmacyclics ❑ NCI, U Texas	Gadolinium texaphyrin (Gd-Tex)	Texaphyrin that selectively accumulates in cancer cells sensitizing them to radiation and detectable by MRI ❑ infusion	Phase Ib/II (o5/97)➢USA ❑ metastatic brain cancer

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Progenics Pharmaceuticals ❑ Memorial Sloan-Kettering Cancer Center, Aquila Biopharmaceuticals, U California, Bristol-Myers Squibb (BMS)	MGV	MGV is a bivalent ganglioside conjugate vaccine composed of two ganglioside antigens, GD2 and GM2, conjugated to an immunogenic carrier protein keyhole limpet hemocyanin (KLH) and combined with the QS-21adjuvant ❑ subcutaneous	Phase I/II (b9/96)➢USA ❑ primary brain cancer
Rhône-Poulenc Rorer	RPR 109881A	Highly potent taxane analog ❑ IV, PO	Phase I (o8/97)➢USA (NCIC-Clinical Trials Group; protocol IDs: CAN-NCIC-IND101, NCI-V96-1096) ❑ adult advanced solid tumors
Sanofi ❑ Southern Research Institute	Tirapazamine ❑ Tirazone	Tirapazamine is a benzotriazine-di-N-oxide bioreductive agent that is selectively activated to a DNA-damaging species in hypoxic tumors ❑ intravenous	Phase II (6/97)➢USA ❑ brain cancer (see FO, p 709)
Schering-Plough ❑ Duke U	Temozolomide ❑ Temodal	Alkalyting agent; imidazotetrazine derivative ❑ PO	MAA (f1/98)➢Europe ❑ recurrent malignant glioma; phase II (o2/98)➢USA ❑ adult relapsed GBM (protocol IDs: SPRI-C94-091, NCI-V95-0651); pediatric recurrent CNS tumors (protocol IDs: SPRI-C94-138-01, NCI-V96-0871, DUMC-114-97-1R2)
Scotia	EF27 ❑ Amelorad	Mixture of fatty acids from evening primrose and fish oils; radioprotectant, radiosensitiser, chemoprotectant	Phase II (discontinued 8/97)➢UK ❑ brain cancer
Seragen	$DAB_{389}EGF$	Recombinant fusion protein in which the receptor-binding domain of diphtheria toxin has been replaced by human epidermal growth factor (EGF) ❑ infusion	Phase I/II (3/97)➢USA ❑ solid tumors expressing EGFr
Serono Laboratories	Recombinant interferon β ❑ Rebif	Cytokine	Phase I/II (4/95)➢USA (under an NCI-investigator IND) ❑ brain cancer
Somatix Therapy (Cell Genesys) ❑ U California at San Diego		Implantation of retroviral producer cells near cancer cells; the producer cells shed retroviral vectors which infect the rapidly dividing cancer cells, rendering them sensitive to a lethal metabolite	Research (4/96)➢USA
Sugen ❑ NCI (CRADA)	SU101	Small synthetic molecule that inhibits the PDGF tyrosine kinase (TK) signaling pathway (structurally similar to leflunomide) ❑ continuous intravenous infusion, subcutaneous	Phase III (b1/98)➢USA ❑ malignant refractory glioma and GBM in first relapse; phase II (03/98)➢USA ❑ newly-diagnosed GBM; phase I (o2/98)➢USA ❑ pediatric refractory CNS malignancies (protocol IDs: NCI-97-C-0087)
Supratek	SP2000	Delivery system based on linking drugs to micelle-forming polymer carriers that may cross the blood-brain barrier	Research (o12/97)➢Canada
Takeda ❑ TAP Pharmaceuticals	Carbamic acid ❑ TNP-470 (formerly AGM-1470)	Fumagillin analog isolated from *Aspergillus fumigatus*, anti-angiogenic, antibiotic ❑ intravenous (IV)	Phase I (o2/98)➢USA ❑ pediatric neuroblastoma (protocol Ids: MSKCC-97072, NCI-G97-1310) also see FO, p 195

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Taiho Pharmaceutical ❑ Kagoshima University, Osaka University Medical School	5-fluoro2'-deoxyuridine (FdUrd)	Fluorinated pyrimidine that is cytotoxic to cells as a consequence of generation of 5-fluoro-2'-deoxyuridylate (FdUMP), a mechanism-based inhibitor of the enzyme thymidylate synthase (TS) ❑ intrathecal	Phase I/II (b1/96)➢Japan ❑ neoplastic meningitis
Targon (Elan and Cytogen jv) ❑ NCI	Phenylacetate ❑ EL-530, NSC-657802	Normal mammalian metabolite; potent differentiating agent	Phase II (b4/95; o2/98)➢USA, Europe ❑ adult malignant glioma and primitive neuroectodermal tumors
Targon (Elan and Cytogen jv) ❑ NCI	Phenylbutyrate ❑ EL-532	Prodrug of phenylacetate	Phase I (o2/98)➢USA ❑ refractory anaplastic astrocytoma, GBM
Techniclone ❑ Cambridge Antibody Technology (CAT)	^{131}I-chTNT-1/B	Chimeric MAb linked to iodine-131 ❑ infusion	Phase I (a3/98)➢USA ❑ GBM and aplastic astrocytoma
Transmolecular ❑ University of Alabama	Chlorotoxin	Toxin obtained from *Leirus* scorpion venom that blocks a glioma-specific choride ion channel that allows chloride and other negatively-charged ions to cross the glial cell membrane	Preclin (12/97)➢USA ❑ malignant glioma
Triangle Pharmaceuticals ❑ U California, San Diego	Alanosine	Toxic aspartate analog derived from *Streptomyces alanosinicus*	Phase II (o3/98)➢USA ❑ brain cancer, glioma
U. S. Bioscience ❑ NCI	Diaziquone ❑ CI-904, NSC-182986 ❑ AZQ	Cytostatic with high CNS bioavailability ❑ intravenous (IV)	Phase III (c97); phase I/II IND (f5/98)➢USA ❑ brain cancer, glioma
University of Pennsylvania	H5.010RSVTK	Recombinant adenovirus for intratumoral transfer of HSV-tk gene	Phase I➢USA ❑ recurrent malignant glioma
VIMRX Pharmaceuticals	Hypericin ❑ VIMRxyn	Chemically synthesized hypericin ❑ PO	Phase II (o2/98)➢USA ❑ GBM
Xenova ❑ Cancer Research Campaign	XR5000	Novel synthetic anticancer; topoisomerase I and II inhibitor IV	Phase I (o12/97) ❑ solid tumors

Source: NEW MEDICNE's Oncology KnowledgeBASE (NM/OK), 1998

ation and halt growth of several malignant cell lines. Bryostatins have been shown to inhibit matrix metalloproteinase (MMP)-1, 3, 9, 10 and 11 production without directly affecting the activity of MMPs, but by inhibiting protein kinase C (PKC). Although the exact mechanism responsible for its antitumor activity is unclear, an initial event in the action of bryostatin-1 is activation of PKC, followed by its down regulation. Tissue inhibitor of metalloproteinase-1 (TIMP-1) levels could also be modulated by bryostatin-1, because TIMP-1 is encoded by a PKC-responsive gene. TIMP-1 has been shown to inhibit tumor-induced angiogenesis in experimental systems (Wojtowicz-Praga SM, etal, Invest New Drugs 1997 15:1 61-75).

One study has demonstrated that bryostatin-1 selectively synergized with IL-2 in triggering monocyte activation, and this effect seemed to be dependent, at least in part, on its ability to upregulate IL-2 receptor γ chain expression. These results indicate that bryostatin-1 is a powerful activator of human monocytes, and suggest that stimulation of monokine secretion by bryostatin-1 may represent at least one of the mechanisms responsible for the *in vivo* antitumor activity of this drug. Monocytes represent a main recognition system for foreign cells, including tumor cells, and play a major role in antigen presentation. Monocytes are also an important source of products exhibiting antitumor and immunomodulatory properties, including interleukin-1 (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor (TNF)-α. (Bosco MC, etal, ASCO97, Abs. 1537:429a).

Phase II clinical trials with bryostatin-1 in recurrent high-grade astrocytomas or mixed gliomas, are being conducted at various cancer centers. Between 12-35 patients are being enrolled (protocol IDs: MDA-NCNSC-96213, NCI-T96-0080, NABTC-NCNSC-96213) and treated with a continuous 24-hour infusion of bryostatin-1, every 8 weeks. Potential side effects include muscle pain and joint aches, a transient decrease in platelets, and release of TNF-α and IL-6 into the blood stream.

Marimastat (BB-2516), under development by British Biotech (Oxford, UK), is a synthetic, low-molecular weight MMPI, characterized by a collagen-mimicking hydroxamate structure, which facilitates chelation of the zinc ion in the active site of the MMP. Marimastat is a second genera-

tion MMPI, is orally available and is currently in phase III clinical trials in the USA, Europe and Canada (Wojtowicz-Praga SM, etal, Invest New Drugs 1997 15:1 61-75). As of March 1997, a randomized, double-blind, placebo-controlled phase III (protocol ID: BB-C03/IVB/131, NCI-V96-0909) clinical trial of marimastat was ongoing involving 150 patients with GBM or gliosarcoma following completion of conventional first-line treatment, including surgery and/or radiotherapy. A phase II clinical trial of gamma knife radiosurgery and marimastat, administered PO *bid* 1 day after surgery and continued until death, disease progression, or drug toxicity (protocol IDs: BB-C03-IVB-172, NCI-V96-1112), to accrue 54 patients, is ongoing.

In late 1996, British Biotech and Tanabe Seiyaku (Osaka, Japan) signed a development and marketing agreement for marimastat in Japan. Tanabe made an initial payment of $7 million, and will pay up to $67 million when marimastat is commercialized. British Biotech will share revenues with Tanabe.

Inhibition of Angiogenesis

Carboxyamide-triazole (CAI), under development by the NCI for treatment of various solid tumors, may also be clinically evaluated in brain cancer. CAI, an inhibitor of selected signal transduction pathways, inhibited proliferation of 6 of 8 glioblastoma cell lines tested in a dose-dependent fashion *in vitro* (IC_{50} range was 1.5-44 μM), with no effect on the U373 line. Incubation with CAI inhibited production of the 72 kDa and 92 kDa type IV collagenases from 16% to 93%, in all cell lines. CAI is consistently able to inhibit the invasive phenotype of all glioma cell lines *in vitro* using the Matrigel barrier assay (IC_{50} range=13-28 μM) (Jacobs W, etal, Journal of Neurooncology, 1997 Apr, 32(2):93-101). At 2-20 μM CAI inhibits Matrigel invasion by glioma cells by 60%, with no effect on cell viability. This regional invasion requires cellular adhesion, local proteolysis and migration which may be inhibited by CAI.

MAb 81C6, a chimeric anti-tenascin MAb linked to iodine-131, developed by Dr. Darrell Bigner at Duke University (Durham, NC), is in phase II clinical trial (protocol IDs: DUMC-221-96-2R3, NCI-H96-0009) in primary or metastatic malignant glioma. Tenascin-C is a glycoprotein of the extracellular matrix whose expression is enhanced in human astrocytomas and correlates with angiogenesis (Zagzag D, etal, Cancer Research, 1996 Jan 1, 56(1):182-9).

Thalidomide, an angiogenesis inhibitor (see FO, pp 275 and 195) under development by EntreMed (Rockfield, MD), advanced to phase II trials in brain cancer in March 1996 at three locations, at Dana-Farber Cancer Institute (Boston, MA), M.D. Anderson Medical Center (Houston, TX) and Vincent Lombardi Cancer Center at Georgetown University (Washington, DC). The trial's initial intent was to treat 15 GBM patients with progressive disease. By October 1996, based on favorable preliminary results, enrollment was increased to 35 patients. This increase in the number of patients was determined in part by evaluating results of MRI scans after finding indications of reduction in tumor size in two of the 15 initial patients. Enrollees were patients with recurring tumors who had been previously treated with radiation therapy and, many, with chemotherapy.

According to results from this phase II clinical trial, reported at ASCO97 by Dr. Howard A. Fine, a neuro-oncologist at Dana-Farber Cancer Institute who was the PI of the brain cancer trials, a 50% response was seen among 32 evaluable patients with progressive GBM and anaplastic gliomas who were treated orally with thalidomide for at least two months; disease stabilized in 12 patients, tumors were reduced by 50% in 2, and tumor size was substantially reduced (less than a 50% reduction) in 2 more. Thalidomide was well tolerated, even in high doses. Eleven patients survived at least one year.

In August 1997, EntreMed reacquired commercial rights to thalidomide from Bristol-Myers Squibb. Under its previous collaborative agreement, BMS retains rights to thalidomide analogs in development and will continue to fund EntreMed R&D in the anti-angiogenesis area but make no milestone payments for thalidomide. In August 1997, EntreMed also renewed BMS warrants to purchase $10 million of its stock. In February 1998, thalidomide was declared an orphan drug for the brain cancer indication.

TNP-470 is an antiangiogenic fumagillin analog isolated from *Aspergillus fumigatus,* under development by Takeda (Osaka, Japan), in collaboration with TAP Pharmaceuticals (Deerfield, IL). When used to treat glial tumors in rats, TNP-470 demonstrated dose-dependent inhibition of 9-L gliosarcoma growth and prolonged survival but caused dose-dependent decreases in body weight (Isobe N, etal al, Anticancer Res 1996 Jan-Feb 16:1 71-6). *In vitro* study of TNP-470 in human medulloblastoma showed it to be an effective treatment agent (Isobe N, etal al, Neuropediatrics 1996 Jun 27:3 136-42). In a phase I clinical trial (protocol IDs: MSKCC-97072, NCI-G97-1310), conducted at Memorial Sloan-Kettering Cancer Center, 12 pediatric patients with neuroblastoma were treated intravenously for ≤1 year with increasing doses MTD.

Vascular endothelial growth factor (VEGF) is another target whose inhibition may suppress angiogenicity and tumorigenicity of GBM. The fact that VEGF plays a major role in GBM angiogenesis was demonstrated by introducing an antisense VEGF-expression construct into glioblastoma cells. As a result of this intervention, VEGF mRNA and protein levels were reduced significantly; the modified cells did not secrete sufficient factors so as to be chemoattractive for primary human microvascular endothelial cells and could not sustain tumor growth in immunodeficient animals; and the density of *in vivo* blood vessel formation was reduced in direct relation to the reduction of VEGF secretion and tumor formation. Moreover, cells that recovered their ability to secrete VEGF regained all tumorigenic properties listed above (Cheng SY, etal, PNAS USA, 1996

Aug 6, 93(16):8502-7). Several developers are exploiting the angiogenic properties of VEGF as a target for cancer therapeutics.

Selective Targeting of Tumor Vasculature

Various approaches are emerging that may allow selective destruction of tumor vasculature by targeting markers exclusive present in tumor cells. This approach may be particularly suited to dealing with GBM, because it is one of the most highly vascularized human tumors. For additional information on anti-vascular approaches, see FO, pp 493-494.

Cell adhesion molecules, selectively present in tumor vessels may provide an effective target of monoclonal antibodies (MAbs) and peptides. Among newer approaches being investigated include targeting the $\alpha_v\beta_3$ integrin that is upregulated in growing tumor vessels (Arap W, Pasqualini R and Ruoslahti E, Science, 16 Jan 1998; 279:377-380), or using antibody fragments that recognize a splice variant (B-FN) of fibronectin present in neoplastic tissues during angiogenesis but not in mature vessels (Neri D, etal, Nature Biotechnology, 15 Nov 1997; 15:1271-1275). Both of these are cell adhesion molecules, pointing to the important role this mechanism plays in tumor metastasis. Treatment strategies are based on linking these molecules with a toxic payload to selectively destroy its target without affecting normal vesculature. Also see FO, p 400.

Exploiting Other Mechanisms

New discoveries and theories about the process of metastasis are being reported at an increased pace as investigators and clinicians target this area as the key obstacle in extending survival of patients presenting with primary malignancies confined to the affected organ. Two newly discovered proteins may shed more light on how malignant brain cells spread and how to prevent them from metastasizing.

Brain-enriched hyaluronan-binding protein (BEHAB), an extracellular hyaluronan-binding protein encoded by the brain-specific BEHAB/brevican gene, was found consistently expressed by human glioma but not by tumors of nonglial origin. BEHAB/brevican which can be cleaved into an N-terminal fragment that contains a hyaluronan-binding domain (HABD) and a C-terminal fragment was shown to be cleaved in invasive human and rodent gliomas. Yale University (New Haven, CT) investigators who discovered BEHAB tested its role in invasion and metastasis by transfecting the noninvasive cell line 9L with either full-length BEHAB/brevican or HABD. Although both constructs increased invasion *in vitro*, only HABD did so *in vivo*. Experimental intracranial tumors from full-length BEHAB/brevican transfectants showed no increase in invasion over controls, whereas tumor invasion from HABD transfectants was significantly potentiated, with new tumor foci emerging at sites distant from the main tumor mass (Zhang H, etal, J Neurosci 1998 Apr 1;18(7):2370-2376).

Glioma-specific chloride channel that permits chloride and other negatively charged ions to pass through the glioma cell membrane, may also play a role in metastasis. Investigators at the University of Alabama (Birmingham, AL) discovered this ion channel exclusively in malignant glial cells. Also, although low grade tumors (e.g., pilocytic astrocytomas), containing more differentiated, astrocyte-like cells, showed expression of glioma chloride currents in concert with voltage-activated sodium and potassium currents also seen in normal astrocytes, high grade tumors (e.g., GBM) expressed almost exclusively chloride currents, pointing to a gradual loss of Na+ currents and gain of Cl- currents with increasing pathological tumor grade (Ullrich N, etal, Neuroscience 1998 Apr; 83(4):1161-1173). Because of its presence in more aggressive tumors, it is theorized that this ion channel makes it possible for malignant cells to spread by regulating the cell's fluid content by promoting salt loss and, therefore, water loss. Fluid loss enables the cell to penetrate through the tight spaces of the extracellular matrix. Use of chlorotoxin, a molecule obtained from *Leiurus* scorpion venom that blocks this ion channel, reduces the metastatic potential of gliomas. A company, Transmolecular (Birmingham, AL), was formed to exploit chlorotoxin as a treatment for GBM.

IMMUNOTHERAPY/VACCINES

Despite the fact that aggressive CNS tumors such as malignant gliomas are "immunologically privileged", exhibiting poor immunogenicity and active immunosuppression, a number of immunotherapy strategies are being attempted with encouraging preliminary results.

Tumor Antigen-specific Cellular Immunotherapy

In preclinical animal studies, antigen-specific (CD4+ and CD8+) T lymphocytes, administered intravenously, rejected tumors growing in the brain. Based on these findings 15 patients with recurrent astrocytoma were treated with a combination of active immunization using Bacillus of Calmette and Guerin (BCG) and specific adoptive cellular immunotherapy using irradiated autologous tumor cells. After 2 weeks of active immunization, a mononuclear cell-rich fraction of blood was obtained by leukapheresis and cultured with irradiated autologous tumor cells and IL-2 which resulted in selective expansion of CD4+ and CD8+ T lymphocytes. These stimulated cells were then administered intravenously to the 15 patients on 24 separate occasions with or without administration of IL-2. Treatment was tolerated with limited toxicity (Holladay FP, etal, J Neurooncol, 1996 Feb 27:2 179-89).

Activated Cytotoxic T Cells

A phase I/II clinical trial (protocol IDs: UCHSC-COMIRB-93426, NCI-T94-00650) has been undertaken using activated cytotoxic T cells in combination with low-dose continuous-infusion of IL-2 (Proleukin; Chiron) in 10 patients with advanced neuroblastoma and recurrent primary brain tumors; the study is to be terminated if severe toxicity occurs in the first 5 patients.

Genetically-modified Tumor Cells

Use of genetically modified tumor cells to express certain cytokines appears to be a viable immunotherapy approach. Researchers have demonstrated the feasibility of efficient gene transduction into primary cultured cells (Wakimoto H, etal, Japanese Journal of Cancer Research, 1997 Mar, 88(3):296-305) but effectiveness of such constructs in humans has not been demonstrated as yet. To determine which cytokine-assisted tumor vaccines would be most effective against CNS, irradiated B16 murine melanoma cells producing murine interleukin 2 (IL-2), IL-3, IL-4, IL-6, interferon (IFN)-γ, or granulocyte-macrophage colony stimulating factor (GM-CSF), were used as subcutaneous vaccines against tumors within the brain. Under conditions where untransfected B16 cells had no effect, cells producing IL-3, IL-6, or GM-CSF increased survival of mice challenged with viable B16 cells in the brain. Vaccination with B16 cells producing IL-4 or IFN-γ, had no effect, and vaccination with B16 cells producing IL-2 decreased survival time. GM-CSF-producing vaccines also increase survival in mice with pre-established tumors. The response elicited by GM-CSF-producing vaccines was found to be tumor-specific and was canceled by depletion of CD8+ cells. Unlike immunity generated against subcutaneous tumors by GM-CSF, however, the effector responses generated against tumors in the CNS were not dependent on CD4+ cells. Therefore, this study suggests that cytokine-producing tumor cells are very potent stimulators of immunity against tumors within the CNS, but effector responses in the CNS may be different from those against subcutaneous tumors (Sampson JH, etal, PNAS USA, 1996 Sep 17, 93(19):10399-404).

Granulocyte-macrophage colony-stimulating factor (GM-CSF)-transduced glioma cells, irradiated and administered by subcutaneous injection, induced a potent immune response against intracranial glioma tumors in a murine model. In one study, GL261 cells were transduced to secrete murine GM-CSF using a retrovirus vector, then irradiated, and injected subcutaneously into mice. GM-CSF was shown to enhance the natural immunogenicity of GL261 tumor cells. MST of animals vaccinated with 5×10^4 or 5×10^5 GM-CSF-transduced cells 7 days prior to tumor cell implantation in the CNS, was associated with a significant increase in survival (45%-50%) and some cures. Antitumor response was as effective whether mice were administered tumor cells 7 days or 14 days after the inoculation. MST of animals treated subcutaneously with 5×10^6 irradiated GM-CSF-transduced cells 3 days after intracranial injection of 2×10^4 nontransduced cells, was extended by 36%. Subcutaneous injection of irradiated GM-CSF-transduced glioma cells induced a potent immune response, which was observed by the presence of CD8+ lymphocytes and eosinophils in intracranial gliomas in the acute phase of tumor rejection. According to these findings GM-CSF-based vaccination is effective both as a preventative against subsequent intracranial glioma cell implantation and for treatment of established intracranial glioma (Herrlinger U, etal, Cancer Gene Therapy, 1997 Nov-Dec, 4(6):345-52).

Immune Response (Carlsbad, CA) has been developing a GBM vaccine, exclusively licensed from Sidney Kimmel Cancer Center (San Diego, CA), that consists of a patient's irradiated glioblastoma cells modified *ex vivo* with an antisense gene that blocks TGF-β expression. These modified cells are then injected subcutaneously into the patient to elicit an antitumor immune response. A phase I clinical trial using this vaccine in the treatment of adult glioblastoma, that was initiated in December 1996 under the direction of Keith Black, MD, then at UCLA, was subsequently put on hold before all 12 patients with GBM were enrolled, when Dr. Black relocated to Cedar Sinai Medical Center (Los Angeles, CA). In the meantime, to expand the applicability of this approach to GBM patients with inextractable glioblastoma cells, fibroblast GM-CSF cell lines that mimic glioma cell lines are being used. The phase I clinical trial is expected to resume in the near future.

Anti-hCG Vaccines

Membrane-associated and cytoplasmic hCG, its subunits, and its fragments were present in cultured human cancer cells from CNS cancers such as brain cancer, neuroblastoma, medulloblastoma, and retinoblastoma. These results correlate with *in vitro* and *in vivo* studies which showed presence of translatable levels of hCG β mRNA in all cancers, including those of the nervous system. These findings establish a scientific basis for use of active and/or passive immunization against hCG for prevention or as a primary adjuvant therapy for cancer of the CNS (Acevedo HF, etal, Cancer Detection and Prevention, 1997, 21(4):295-303). However, the role of hCG in cancer immunotherapy remains controversial.

Administration of Growth Factors/Cytokines

Chemo-immunotherapy using systemically-administrated cytokines, such as IL-2 and/or IFN-α, in combination with standard chemotherapy, may prove effective in treatment of cancer that has metastasized to the brain. In a prospective study conducted between September 1992 and June 1994 in patients with melanoma brain metastasis (MBM), two monthly induction cycles consisting of CDDP (100 mg/m^2) on day 1, rIL-2 (18 MUI/m^2) delivered by a 24-hour intravenous infusion on days 3-6 and days 17-21, and simultaneous subcutaneous injection of IFN-α (9 MUI) 3 times weekly, were followed by 4 monthly maintenance cycles with CDDP, daily subcutaneous IL-2 (5 MUI/m^2) from days 15 -19 and 22-26, and IFN-α (9 MU) 3 times weekly, repeated every 5 weeks. The median follow-up was 34 months (range=22-54). Among 13 evaluable patients, the objective response (OR) rate was 39% (1 CR and 5 PR) lasting for 29 weeks (range=11-50); disease stabilized in two patients. Overall median survival was 32 weeks (51 weeks for those with OR or SD and 37 weeks for those with progressive disease). Toxicity included nausea,

vomiting and diarrhea and nearly all patients experienced hypotension and fever. Because of careful attention to fluid balance, no one experienced weight gain and there was only one case of Grade 3 renal toxicity, and one case of reversible cerebral edema. In view of the response rate and prolonged survival, this treatment appears as an alternative to radiotherapy or chemotherapy alone in selected patients with MBM (Mousseau M, etal, ASCO97, Abs. 1773:492).

"SUICIDE" GENE THERAPY

In "suicide" gene therapy cancer cells are selectively transfected with suicide genes that confer a vulnerability to a certain drug that is non-toxic to unstransfected cells. In this manner, a suicide gene may be introduced either intratumorally, or systemically in a form that is taken up and expressed selectively only by tumor cells. The drug is then introduced systemically and affects only the transfected tumor cells. However, untransfected cells in the vicinity of transfected cells are also killed by a process referred to as the bystander effect which may improve the efficacy of the construct if these cells are malignant but also cause toxicity if they are normal.

The most common suicide gene is the one that encodes herpes simplex virus-thymidine kinase (HSV-tk) that sensitizes cells to the antiviral drug ganciclovir. Although most approaches in clinical development in brain cancer are using retroviral vectors as delivery vehicles, recombinant adenovirus transfer of the HSVtk gene followed by ganciclovir may also be applicable as an *in situ* treatment for tumors (Smythe WR, Cancer Research, 1994 Apr 15, 54(8):2055-9 and Annals of Surgery, 1995 Jul, 222 (1):78-86).

To date clinical trials produced no cures and the technique has been embraced by some but dismissed by others.

Adenoviral Vector-mediated Transfer

IntroGene (Leiden, the Netherlands) is conducting a phase I clinical trial of HSV-tk gene therapy in patients with glioma (IGN-HSVtk-GL-06) and leptomeningeal metastases (IGN-HSVtk-LM-06). IntroGene is using a novel adenoviral-vector-producing cell line, PER-C6, to package the gene for delivery. PER-C6 delivers genes free from contamination with replication competent adenovirus.

University of Pennsylvania Medical Center (Philadelphia, PA) researcher Steven L. Eck, MD, has constructed a recombinant adenovirus, H5.010RSVTK, to mediate intratumoral transfer of HSV-tk gene into primary human brain tumors. In a phase I clinical trial involving 13 adult patients with recurrent malignant glioma that concluded recently, patients were treated for 14 days with stereotactically-guided intratumoral injections of the virus, followed by intravenous administration of ganciclovir. Patients eligible to undergo palliative debulking were treated in a similar fashion followed by resection on day 7. At resection, a second dose of virus was administered intraoperatively directly to the unresectable residual tumor, with intravenous ganciclovir continued for 14 more days (Eck SL, etal, Human Gene Therapy 1996; 7(12):1465-82). Results were promising with one patient demonstrating no evidence of tumor at 10 months post-treatment. Phase I/II trials will commence in April 1998, with additional phase I clinical trials planned to asses increased dose levels and number of injection sites. Development of this agent is currently being funded by the NCI.

Parvoviral Vector-mediated Transfer

Avigen (Alameda, CA) is applying its adeno-associated virus (AAV) vector approach to develop therapeutics for malignant glioma. Avigens's AAV vectors are derived from the naturally occurring parvovirus by recombinant DNA techniques. The viral genome extracted from the virus is cloned into a plasmid to facilitate its modification. Subsequently, these viral vectors are modified by replacing the rep gene which directs production of the proteins that enable the virus to replicate its genome and integrate into a specific site on human chromosome 19 and the cap gene which directs production of the protein coat that encases the viral genome. These two viral genes are bound by two short identical stretches of DNA, inverted terminal repeats (ITRs), that are required for integration and genome replication and also contain instructions for insertion of the viral genome into the protein coat. The viral rep and cap genes are removed and replaced by a gene cassette bound by the viral ITRs. Finally, the resulting vector plasmid is introduced into packaging cells in tissue culture along with a helper plasmid containing the rep and cap genes. Avigen's proprietary manufacturing process has eliminated the need for a helper virus so that there is no risk of adenovirus contamination of the final product. Avigen's manufacturing process also results in substantially increased yield of AAV vector.

Preclinical studies have demonstrated the efficacy of AAV vector-based gene therapy in GBM in animal models. AAV vectors deliver and achieve simultaneous expression of the tk and IL-2 genes in tumor cells *in vitro*. Following a single injection of an AAV-tk vector into brain tumors arising in mice from human glioma cell xenografts, a significant reduction in tumor size was observed in all animals that were also treated with ganci-clovir. There was also evidence of a bystander effect that resulted in the death of tumor cells in contact with the transfected cells (Okada H, etal, Gene Therapy, 1996, 3:957-964).

In September 1997, the University of California awarded a grant to Avigen as part of the Biotechnology STAR Project, aimed at developing gene therapy approaches to cancer therapy using Avigen's AAV vector technology. Work performed under the grant will focus on developing and refining an AAV vector system for use in treating brain tumors. The grant provides matching funds of $68,166 over two years for research in the University of California, San Francisco laboratory of Mark Israel, MD, an Avigen scientific advisory board member.

Retroviral Vector-mediated Transfer

Retroviral vector gene transfer is attractive because these viruses transport their own genetic information into the genome of transfected cells conferring a longer-lasting and more stable expression than adenoviral vectors. However, titers of these vectors are low either requiring *ex vivo* cell transfection or co-injection of helper producer cells to ensure a continuing source of *in vivo* vector production. For instance, only limited efficacy was observed when U-87 or C6 gliomas were co-implanted in nude mice with retroviral producer cells (VPC) that expressed HSV-tk gene and treated with ganciclovir. Tumors from C6 cells carrying the HSV-tk gene were sensitive to, but not killed by GCV. The ineffectiveness of the HSV-tk/GCV system in glioma gene therapy may be attributable to insufficient gene transfer and/or delivery of GCV to glioma cells. A combination of HSV-tk and IL-4 proved more effective than either approach alone. Co-injection of IL-4 VPC and C6 cells in immunocompromised rats was also effective in inhibiting growth of C6 brain tumors, producing a 38% survival rate lasting for at least 2 months (Benedetti S, etal al, Hum Gene Ther 1997 Jul 20 8:11 1345-53).

Chiron (Emeryville, CA) is also evaluating, in a phase I clinical trial (MGH-H97-1122, NCI-H97-1122), treatment of adult recurrent malignant glioma using a retroviral vector delivery of the HSV-tk gene with subsequent treatment with ganciclovir. In this dose escalation study, to enroll 27 patients, three different protocols of VPC HSV-tk stereotactic injections are used (VPC injected into three areas of tumor at biopsy, VPC injected *bid* for two weeks or VPC injected into tumor periphery *bid* for 2 weeks), all involving systemic treatment with ganciclovir.

Genetic Therapy (Gaithersburg, MD), a Novartis subsidiary, is developing GLI 328, a gene transfer construct that delivers the HSV-tk gene by means of a retrovirus vector. A phase II multicenter trial designed to determine the safety and efficacy of repeated intratumor injections of GLI 328 in patients with recurrent glioblastoma, was conducted at the University of California, San Francisco. All patients had surgically resectable well-defined tumors that were not located in the deep nucleus, the corpus collosum, or adjacent to the ventricle. The treatment strategy involved surgical removal of the tumor on day 0, and injection of GLI 328 on day 7. Injections were administered at multiple sites over a grid of suture material laid down on the walls of the surgical cavity produced after removal of the tumor. GCV was administered from day 21 to 35 and, on day 41, patients were evaluated by MR scan. If the scan indicated stable disease or improvement, patients underwent another cycle of treatment. Twenty-nine eligible patients were treated with this protocol. Transient expression of vector sequences in peripheral leukocytes, with no evidence of replication-competent virus, was seen in one-third of cases. Twenty-seven patients died; 22 died of disease progression and 5 from pulmonary emboli. Two were still alive 32 and 38 months after treatment. MST of treated patients was 8 months, which exceeded the 3-month survival typical of untreated patients, although it was similar to MST achievable with chemotherapy.

The one serious adverse effect was a severe ventricular and meningeal inflammation syndrome which occurred in 3 patients. It was believed that it occurred because of the accidental rapid injection of the gene therapy vector into the ventricle. Thirteen patients also experienced mild transient symptoms of headache and confusion that were associated with local necrosis, inflammatory infiltration and the presence of cytotoxic T lymphocytes. A humoral immune response was seen in the form of production of antibodies to the viral capsid in 10 patients and to VPC in half the patients. Ongoing studies are investigating the possible role of humoral immune responses in the cytotoxic response to this therapy.

In a multicenter phase III trial, initiated in Europe on July 15, 1996, 233 newly diagnosed GBM patients are being treated by surgery followed by a combination of radiation and GLI 328. The trial is expected to be completed in June 1998.

The results of the clinical trials indicate that GLI 328 is well-tolerated, so long as it is not injected into the ventricle. Its effectiveness is similar to other aggressive local therapies and it also induces an immune response. Questions for future trials include whether this approach is safe in tumors near the ventricles, if there is a prognostic significance of the immune response, and if this treatment may play a role in treating invasive and/or multifocal tumors.

MONOCLONAL ANTIBODIES

Lexigen Pharmaceuticals

Lexigen Pharmaceuticals (formerly Fuji Immuno-Pharmaceuticals; Lexington, MA) is developing an anti-GD2 antibody (ch14.18) for the treatment of neuroblastoma. Initial development of this construct began at Damon Biotech, which was merged into Abbott Laboratories in 1992. This MAb was humanized in collaboration with Scripps Research Institute (La Jolla, CA) and the University of California at San Diego (USCD) Cancer Center (La Jolla, CA). It is currently in phase III clinical trials in Europe for the indication of neuroblastoma and similar trials are anticipated to begin in the USA sometime in 1998. It has orphan drug status for neuroblastoma in the USA.

Murine MAb14.G2a recognizes GD2, a disialoganglioside expressed in tumors of neuroectodermal origin, and facilitates antibody-dependent cellular cytotoxicity (ADCC) *in vitro*. Also, interleukin-2 (IL-2) administered *in vivo* increases ADCC by enhancing the number and activity of circulating lymphocytes (Frost JD, etal, Cancer 1997 Jul 15 80:2 317-33). Lexigen intends to develop a fusion protein of MAb14.G2a and IL-2.

The therapeutic efficacy of anti-GD2 MAb for neuroblastoma is believed to be primarily attributable to ADCC. Because GM-CSF may enhance ADCC of granulocytes and monocytes and raise the number of these cells, a phase II clinical trial (POG9347) of ch14.18 was undertaken in com-

bination with GM-CSF in pediatric recurrent or refractory neuroblastoma. Treatment consisted of a 5-hour daily infusion of ch14.18 (50 mg/m^2) for 4 days and daily injections of GM-CSF (10 pg/kg) for 14 days. Altogether, 70 treatment courses were administered to 32 patients who had failed 1 to 4 regimens of therapy, including 18 previously treated with bone marrow transplantation (BMT). Side effects were tolerable and reversible, with pain, fever and tachycardia occurring in almost all patients. A mild and transient thrombocytopenia peaked on day 4 and resolved by day 7. Among 27 patients evaluable for response, there was 1 CR, 3 PR, 1 mixed response, and disease stabilized in 2. Among the 5 responding patients, 1 died of relapse at 16 months, and 4 were alive at follow-up of 9, 17, 18 and 20 months. There was an increase in the neutrophil-mediated ADCC activity to >20 lytic unit (LU) in all responding patients (Yu AL, etal, ASCO97, Abs. 1846:513).

Although systemic infusion of ch14.18 appears promising for the treatment of pediatric neuroblastoma, it is accompanied by severe pain and altered cardiovascular tone. Change in nociceptive threshold produced by anti-GD2 antibody was examined in rats administered bolus injections of antibody through an indwelling jugular catheter. At high doses, allodynia began within the first 15-minute test interval, was maximal within the first hour, and at some doses was still present, although greatly reduced, at 24 hours and 48 hours. Rapid administration of antibody led to a mean 12 mmHg ±1.8 increase in resting blood pressure and development of prolonged cardiovascular response to an innocuous stimulus (Slart R, etal, Pain 1997 Jan 69:1-2 119-25). Pain is controllable with moderate to relatively high doses of IV morphine. Also, IV lidocaine may be used as part of the analgesic regimen accompanying anti-GD2 antibody treatment (Xiao WH, etal, Pain 1997 Jan 69:1-2 145-51).

Techniclone

Techniclone is developing ^{131}I-chTNT-1/B, a radioactive chimeric MAb construct for treatment of some forms of malignant glioma. The drug delivery system employed in ^{131}I-chTNT-1/B is based on the use of MAbs to anchor a toxic payload, in this case a radioactive isotope, to the necrotic core of solid tumors, thereby permitting destruction of tumors from the inside out, without damaging surrounding healthy tissue. The MAb targets and anchors on double stranded DNA and a histone complex within the cell nucleus which are highly stable, do not modulate and do not disappear. These targets provide abundant antigen and can be exploited for ^{131}I-chTNT-1/B targeting of necrotic cells. Healthy membranes of normal cells cannot be penetrated by the large antibody molecule and, therefore, this construct does not anchor to, or adversely affect, healthy tissue. In preclinical trials ^{131}I-chTNT-1/B anchored equally well onto most solid tumors because the DNA binding site is identical in all cells, even though it is accessible only in necrotic/dying cells.

Techniclone is collaborating on the development of ^{131}I-chTNT-1/B with Cambridge Antibody Technology (CAT; Royston, UK). The joint venture, initiated in February 1996, involves development of both chimeric and human MAbs for tumor necrosis therapy (TNT). Except for Techniclone's manufacturing rights to TNT, all revenues and costs are shared equally between Techniclone and CAT.

In March 1998 Techniclone received FDA clearance to begin phase I clinical trials with ^{131}I-chTNT-1/B in the treatment of malignant glioma. ^{131}I-chTNT-1/B will be administered as a 24-hour continuous infusion through a stereotactically placed intratumoral catheter. This low-pressure intra-tumoral catheter delivers therapeutic agents to large regions of the brain by increasing bulk flow and producing interstitial convection. Advantages of this delivery system include bypassing the BBB, high local drug concentration in the tumor resulting in increased drug uptake, and less systemic leaking of antibody. The study is expected to enroll up to 24 patients with recurrent supratentorial anaplastic astrocytoma and GBM who are candidates for surgical treatment. Endpoints in the study include safety, determination of MDT, pharmacokinetic profile, and radiation dosimetry.

NOVEL POTENTIAL TREATMENTS DRIVEN BY NEW GENE DISCOVERIES

Numerous markers (see FO, pp 690-693) have been linked to CNS cancer and may serve as the basis for diagnostic, prognostic and therapeutic strategies. One such recent discovery of a gene associated with brain cancer is already the subject of a multimillion dollar deal. In April 1997 Myriad Genetics (Salt Lake City, UT) entered into an agreement with Schering-Plough to develop treatments based on five genes, two involved in prostate cancer and, one, the mutated multiple advanced cancers-1 (MMAC-1) gene, linked to brain as well as kidney, prostate, breast and skin cancer. The agreement which specifies a three-year research program that may be extended for another two years, may be worth up to $60 million, consisting of $4 million in equity investment, $21 million in R&D contributions, and $35 million in milestone payments, excluding royalties. Schering retains exclusive worldwide rights to all drugs and Myriad to all diagnostic products and services resulting from the collaboration.

Sequencing of this gene, associated with progression of brain cancer to GBM, was announced simultaneously in late March 1997, by Myriad Genetics, in collaboration with M.D. Anderson Cancer Center, and by Columbia University College of Physicians and Surgeons (New York, NY) in collaboration with Cold Spring Harbor Laboratories (Long Island, NY). Originally dubbed BCN1 by Myriad, it was subsequently renamed MMAC-1 when it was discovered to be involved in other cancers in addition to brain cancer. The Columbia team named this gene P-Ten and is negotiating a licensing agreement with Tularik (South San Francisco, CA).

The discovery and sequencing of this gene is particularly significant because it belongs to a group of genes whose malfunction influences transition to the malignant state. When it functions normally the gene produces a cellular enzyme that signals a cell to stop dividing. Brain cells progressing to malignancy may incorporate a defective version of this gene and do not produce the enzyme.

DELIVERY OF THERAPEUTICS TO THE BRAIN

Electroporation for Delivery of Genes

Genetronics (San Diego, CA) is using electroporation to deliver genes into certain tissues including brain tumors. Advantages of delivering genes by this non-viral method, in addition to high efficiency, include the possibility of introducing very large genes, including whole genes, which may be necessary to cure certain single gene diseases. In November 20, 1997, at the 6th International Conference on Gene Therapy of Cancer held in San Diego, Dr. Ken Dev of Genetronics and a collaborating team headed by Dr. Toru Nishi, at Kumamoto University School of Medicine (Honjo, Japan), reported highly efficient gene transfer and expression of at least 100 times better than simple injection without electroporation, of tow marker genes into subcutaneously implanted glioma tumors in rats. Results demonstrated the potential of *in vivo* electroporation of DNA for gene therapy of solid tumors in the brain and elsewhere. Transfer was accomplished by injecting the gene into the tumor and applying a very short, pulsed rotating electric field to the tumor by means of insertion of a special array of needles and use of an optimized combination of voltage and pulse duration. Confocal microscopy of tumor tissue slices, using a green fluorescent marker gene, showed uptake of genes by an extremely high percentage of cells in the tumor tissue.

Currently, research is in progress to deliver functional genes into brain tumors. With electroporation, no helper cell line is required, the danger of mutation is decreased, and adverse immune reactions are minimized compared to gene delivery by the most common viral vectors currently used in clinical trials for gene therapy. Also, quality control of viral particles for *in vivo* administration is laborious and expensive. Genetronics' much simpler, less costly technique can be used in both dividing and non dividing cells.

Crossing the Blood-Brain Barrier (BBB)

Cereport (receptor-mediated permeabilizer-7 or RMP-7), under development as by Alkermes (Cambridge, MA), is a nine amino acid peptide based on bradykinin that temporarily increases the permeability of the BBB. It is currently being clinically evaluated as an intra-arterial or IV treatment, in combination with carboplatin, in various clinical trials.

As of October 1997, Alkermes had conducted four phase II clinical trials of RMP-7 and carboplatin involving 600 adults with recurrent malignant glioma. In December 1996, Alkermes announced results concerning two of three non-controlled, open label phase II clinical trials conducted in Europe. The first study enrolled patients with recurrent malignant glioma who had relapsed following treatment with surgery and radiation, and the second included patients who had relapsed following treatment with surgery, radiation, and chemotherapy. Response to treatment, as measured by three standardized tests of neurological impairment and patient performance status, was 61%-91% and 40%-59% for the two studies, respectively. Also, 79% and 24% of patients, respectively, responded to treatment as measured by shrinkage or stabilization of tumor volume as confirmed with contrast-enhanced MRI.

In March 1997, interim analysis of a third 121-patient multicenter, blinded, placebo-controlled phase II clinical trial, conducted in the USA, that compared the combination of carboplatin with RMP with that of carboplatin and placebo, indicated that the study had failed to meet its primary endpoint, i.e., time to tumor progression as measured by MRI scanning. The study was designed to include multiple additional endpoints such as MST, six-month survival rate and slowed progression of functional impairment. Results regarding these endpoints have not been reported to date. A fourth non-controlled, open label multicenter phase II clinical trial of RMP-7 and carboplatin, administered intra-arterially, was still ongoing in the USA as of late 1997.

Because results from the phase II clinical trials could not support an early NDA filing, in January 1998, Alkermes announced it will initiate a 250-patient phase III clinical trial in primary glioma in the first quarter of 1998. This phase III trial will compare RMP-7 plus carboplatin with carboplatin monotherapy. The primary endpoint is survival. Patients are to be recruited after undergoing surgery but before radiation treatment, and will be treated with four cycles of chemotherapy.

In October 1997, Alkermes formed a 50/50 partnership agreement with Alza to further develop Cereport. Under terms of the agreement Alkermes may receive up to $60 million from Alza, that already owns 10% of Alkermes. The deal involves an upfront payment of $10 million by Alza, plus research funding estimated at $30 million, and a payment of $10 million to $20 million if the drug is commercialized, with the final amount adjusted to ensure that Alkermes and Alza would have spent equal amounts on research. Alkermes will be responsible for manufacturing the drug and the two companies will share equally in any profits.

SP2000 Biotransport, under development by Supratek Pharma (Montreal, Canada), is a drug delivery system that may be useful in transporting drugs across the BBB. This approach covalently attaches drug moieties to micellar-forming polymer carriers. The resulting complexes are stable with long circulating times and preserve the drug's activity. In an experimental model, SP2000 system effectively penetrated cell membranes, indicating it may target drugs to sites made inaccessible because of hydrophopic barriers such as the BBB.

MEETING COVERAGE

ADVANCES IN THE MANAGEMENT OF GASTROINTESTINAL CANCER

FROM THE 62ND ANNUAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG) CHICAGO, IL; NOVEMBER 3-5, 1997

BARRETT'S ESOPHAGUS

Prevalence of Short-Segment Barrett's Esophagus (SSBE)

Over the last ten years, there has been a significant increase in the number of patients presenting with short-segment Barrett's esophagus (SSBE), a disorder characterized by an abnormally appearing esophageal epithelium less than three centimeters in length on endoscopy and replacement of normal epithelium by intestinal type (intestinal metaplasia) on biopsy. SSBE, now as common as long-segment Barrett's esophagus (LSBE), has been associated with adenocarcinoma of the esophagus. Although incidence of adenocarcinoma in prospective series in SSBE is yet to be determined, data from one surgical program documented that 38% of adenocarcinomas of the esophagus and esophagastric junction associated with Barrett's esophagus were found in Barrett's less than three centimeters long. Also, prevalence of SSBE is about 10% in patients undergoing upper endoscopy for any indication, with the presumptive pathophysiology being gastroesophageal reflux disease (GERD). It is now well founded that dysplasia can occur in SSBE, and like LSBE, SSBE tends to be a disease of white males.

Diagnosis and Treatment of SSBE

Management of SSBE is the same as that of LSBE. Proton pump inhibitor therapy using an agent such as omeprazole (Prilosec; Astra Merck), has been demonstrated to be appropriate for total control of symptoms caused by GERD. Given the occurrence of dysplasia and the possible development of cancer in SSBE, surveillance endoscopy and biopsy are considered appropriate management strategies. If there is no dysplasia on two consecutive endoscopies, then surveillance is carried out every three years. If low grade dysplasia is confirmed, surveillance endoscopy, should be carried out twice annually. Selective resection is recommended in patients with high-grade dysplasia (Sampliner RE, "Back To The Future of GERD", symposium presented during ACG97, pp 31-37).

PREVENTION AND TREATMENT OF ESOPHAGEAL CANCER

Photodynamic Therapy

Barrett's dysplasia may be treated effectively using photodynamic therapy (PDT) that appears to be a safe and effective alternative to esophagectomy, destroying dysplastic mucosa in Barrett's esophagus in 77% of cases and, either along or in combination with the ND:YAG laser, eliminating Barrett's mucosa completely in 37% of cases. PDT, using porfimer sodium (Photofrin; QLT PhotoTherapeutics) as the photosensitizer, was used to treat 62 patients with Barrett's esophagus and dysplasia. Light (630 nm) was delivered endoscopically using a diffuser or by a centering balloon technique. Follow-up endoscopies to identify residual Barrett's mucosa were carried out in 6 to 20 months after treatment. All patients were maintained on omeprazole (20 mg) *bid* for three months, and then daily for nine months. Dysplasia was eliminated in 48 patients and Barrett's mucosa in 23. Approximately 75% to 80% of treated areas healed with squamous mucosa. Strictures developed in 45% of patients, although recent studies with 5 and 7 cm balloons reduced such incidence to 18%. There was no mortality (Haydek JM, etal, ACG97, Abs. P349:456).

Refractory adenocarcinoma of the distal esophagus, may also be palliated with PDT. Eight patients with this condition and severe dysphagia who were not candidates for conventional therapy because of medical co-morbidities, were treated with PDT for symptom palliation. Treatment consisted of IV porfimer sodium (2.0 mg/kg) on day one, followed by endoscopy on days three and five to expose the lesions to laser light (Laserscope Surgical System) therapy at a wavelength of 630 nm. Laser light was delivered via a 2.5 cm cylindrical diffuser at a dose of 300 J/cm^2. During a mean follow-up period of four months (range=1-6), there were no deaths. All patients responded to therapy, with 6 of the 8 experiencing complete relief from dysphagia although 2 of these experienced a benign stricture secondary to PDT which responded to dilation; the remaining 2 experienced PR. There was no weight loss in anyone of the group following therapy, and a mean weight gain of seven pounds was recorded (Kauffman J, etal, ACG97, Abs. P168:322).

Beta-carotene can effectively prevent light-induced dermal injury after profimer sodium injection in patients undergoing PDT, without compromising this treatment's desired effects. To study the dermal protective effect of beta-carotene, 3 patients undergoing PDT for esophageal cancer were treated with profimer sodium (2 mg/kg) on day 0 and, at the same time, they also were started on a 15-day course of beta-carotene (60 mg) administered orally four times daily; PDT was performed on days 2 and 4. Patients wore a thick brown paper bag with a one square-inch window on their hands. The dorsal surface of the hand was then exposed to sunlight 5, 7, or 15 days after profimer sodium injection. After exposure, hands were examined at one, six, 24, and 48 hours and local symptoms (itching, burning, or pain) and signs (erythema, swelling, or blistering) were recorded by the patients; a physician also examined the affected areas within 48 to 72 hours of exposure. There was a fivefold to tenfold increase in serum beta carotene levels in all patients and none developed any dermal injury. Also, the expected local response on upper

endoscopy during the second PDT session was experienced by all patients, with dysphagia improving in all (Khan NA, etal, ACG97, Abs. P110:280).

Stents

Self-expanding metal stents provide an effective palliative treatment in patients with malignant esophageal strictures. Survival or cost associated with stent placement does not appear to be significantly influenced by advanced age nor presence of distant metastases, albeit it appears that the cost-benefit ratio may diminish in those with distant metastases, in view of an expected short survival. A study, to evaluate use of metal esophageal stents in elderly patients or those with distant metastases, in terms of patient survival and stent cost per day, enrolled 24 consecutive patients fitted with metal stent inserts for malignant esophageal strictures (McIntosh AS, etal, ACG97, Abs. Pl78:330).

Three different stent types of varying length and diameter were used, such as Wallstent (n=16), Ultraflex (n=6), and EsophaCoil (n=2), with a price range of $1,195 to $1,895. Wallstent Esophageal II Endoprosthesis, developed by Schneider (Minneapolis, MN), a Pfizer company, has been available since 1994. EsophaCoil, marketed by InStent (Sunnyvale, CA), a subsidiary of Medtronic (Minneapolis, MN), is a self-expandable, nickel-titanium coil stent that can be inserted under topical anesthesia. Ultrastent is supplied by Boston Scientific (Watertown, MA).

Median survival time (MST) of all patients was 67 days (range=4-413 days). All four remaining alive at 111, 224, 353, and 413 days post-stent placement were free of distant metastases and two were >70 years-of-age. Imaging studies were performed in 22 patients to determine distant metastases. Results were as follows:

	Patients (#)	MST (days)	Mean Stent Cost per Day ($)
Total	24	67	54.80
With distant metastases	9	64	92.00
Without distant metastases	13	105.2	35.20
>70 (mean=79.5)	10	124.2	66.40
<70 (mean=58.2)	14	78.6	46.60

GASTRIC CANCER

Neoadjuvant Chemotherapy

To assess the possible usefulness of neoadjuvant chemotherapy with 5-fluorouracil, leucovorin, Adriamycin, and cisplatin (FLAP) in gastric cancer, 9 patients, all with at least T3 tumors pre-therapy, were treated with one, and later, two cycles of FLAP and then restaged prior to attempting a curative gastric resection. All patients underwent gastrectomy and 7 with transmural tumor and/or nodal metastases, underwent intraoperative radiation therapy, at a dose of 1000 cGy, followed by postoperative radiation therapy. There was no operative mortality. Histologically, all patients had tumor-free margins. One patient experienced a pathologic CR, 5 had lymph node metastases, while in 2 of the 9 (22%) the lymph nodes were filled with mucous only, suggesting killing of previously viable tumor. With a median follow-up of 13 months, 7 of 9 patients remained free of disease for a period of 4-29 months (Stiller G, etal, ACG97, Abs. P367:469).

COLORECTAL CANCER

Benefits of Screening

An analysis of the lifesaving benefits of colorectal cancer screening pointed out that without proper screening colorectal cancer decreases life expectancy by more than eight months for adults in their early 50s. A mathematical model, declining exponential approximation of life expectancy (DEALE), was used to calculate the effects of disease on the length of life, based on population statistics provided by the USA government in conjunction with annual deaths from colorectal cancer and published reports estimating decreases in mortality of colorectal cancer attributable to various screening modalities.

Screening using fecal occult blood tests, flexible sigmoidoscopy or colonoscopy, was assumed to decrease mortality from colorectal cancer by 18%, 30%, and 59%, respectively. When life expectancy with and without screening were compared, it was concluded that colorectal cancer decreases life expectancy by 246 days in those aged 50 to 54 and by 58 days in those aged 70 to 74. Colonoscopy screening results in an extended survival that is twice as long as that of flexible sigmoidoscopy and thrice as long as that attributable to annual fecal occult blood tests. Screening based on colonoscopy would increase life expectancy by almost five months for adults aged 50 to 54 years and by 35 days for those aged 70 to 74 years (Inadomi JM and Sonnenberg A, ACG97, Abs. 38:179).

Colon Cancer Prevention

Difluoromethylornithine (DFMO), under development as Ornidyl by Ilex Oncology (San Antonio, TX) may be useful in colon cancer prevention, leading to a decreased risk of colon cancer.

Data from a phase II a clinical trial indicates that continuous suppression of polyamine levels in rectal mucosa of those with a prior history of resected colon polyps, may be accomplished by using very low doses of DFMO that can be delivered with an excellent safety profile. This study enrolled 119 healthy subjects, between 40 and 80 years-of-age, who have had colonic polyps removed during the prior five years. Enrollees were randomized to one of four oral daily doses of DFMO (0, 0.075, 0.20, or 0.40 gm/m^2) for one year. Baseline and serial audiometry, rectal mucosa polyamine levels, and symptom monitoring were performed over a 15 month period. There was no apparent difference between symptoms or audiograms in any patients

in the four groups at any time. DFMO treatment inhibited putrescine levels in a dose-dependent manner, an effect that was evident at six months and showed a consistent proportionate decrease with each equally sized dose increment. At a dose of 0.4 gm/m^2, these levels decreased to approximately 10% of those in the placebo group. Similar results were seen in the sperimidine/ spermine ratio. All polyamine levels returned to baseline after discontinuation of DFMO (Pelot D, etal, ACG97, Abs. P226:365).

Aspirin, at low doses, may be effective for primary prevention of colorectal cancer in the general population and result in an increase in life expectancy. Aspirin has been clearly shown to reduce mortality from both colorectal cancer and myocardial infarction (MI), as well as peptic ulcer disease. The effect of low-dose, once-daily aspirin (325 mg) on the life expectancy of the general population was evaluated using the DEALE mathematical model and 1993 USA population statistics. Effects of low-dose aspirin on colorectal cancer, MI, peptic ulcer disease and stroke were based on the Nurses' Health Study, Physicians' Health Study, and Antiplatelet Trialists' Collaboration.

Aspirin protection against colorectal cancer increased life expectancy by 14.7 days per person if treatment begun at age 25 and by 19 days if it started at age 35. After factoring in beneficial changes in mortality from MI and peptic ulcer disease attributable to aspirin, this therapy, when initiated at age 25 and 35, would result in increases in individual life expectancy of 76.6 days and 99.9 days, respectively. These large benefits persisted after sensitivity analysis (Roy HK, etal, ACG97, Abs. P403:494).

Argon Plasma Coagulation of Colorectal Adenomas

Argon plasma coagulation (APC), a thermal modality adapted for use with flexible endoscopy, is safe and effective for abating residual adenomatous tissue at the polypectomy base, in patients with large colorectal adenomas (benign neoplasms of epithelial tissues). While the expected incidence of recurrent or residual polyps in these cases was 100%, APC resulted in complete ablation of adenoma in half of treated cases, based on an analysis of outcomes of 56 polypectomies involving large colon polyps with or without the use of APC, over a period of two years. All polyps were sessile. APC was used to treat the base of the polyp if complete endoscopic removal was not achievable. APC was used following 28 piecemeal polypectomies, while 38 were performed using standard techniques. At six months follow-up after the initial procedure, colonoscopy was performed to check for residual adenomatous tissue. Although there were no recurrences in 50% (14/28) of the APC group and 50% (19/38) in the standard technique group, APC was associated with a decrease in the incidence of postpolypectomy bleeding which occurred in 3.5% of APC-treated cases compared with 15% in the standard technique group (Zlatanie J, etal, ACG97, Abs. P415:502).

ADVANCES IN THE MANAGEMENT OF HEMATOLOGIC DISORDERS

FROM THE 39TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY; SAN DIEGO, CA; DECEMBER 5-9, 1997

ACUTE MYELOGENOUS LEUKEMIA (AML)

Maxamine and IL-2 Combination Therapy

Outpatient (home) treatment with histamine dihydrochloride (Maxamine; Maxim Pharmaceuticals), in combination with interleukin-2 (IL-2) immunotherapy, is proving to be a unique, safe, and effective approach to protect against relapse and, thus, prolong survival of patients with AML. In a phase IIb clinical trial, 28 AML patients [17 in first CR (CR1), 8 in CR2, 2 in CR3, and 1 in CR4] were treated subcutaneously with IL-2 (1.0 µg/kg) and Maxamine (0.3 to 0.7 mg) twice daily, in repeated courses of 21 days until relapse or CR lasting 24 months. Cytarabine (Cytosar-U; Pharmacia & Upjohn) and thioguanine in low doses were administered between initial courses of immunotherapy. At 20 months median follow-up, 12 of 17 (70.6%) CR1 patients remained in CR up to 20+ months. At 29 months median follow-up, in 11 evaluable patients in CR greater than one, 5 (33%) remained in remission and 8 of 10 (80%) reached a duration of CR exceeding that of the previous CR. In these patients the expected survival of 9.5 months in CR1 was extended to 26.5 months (Brune M, etal, ASH97, Abs. 2253:506A). Multicenter phase III clinical trials in AML began in February in the USA, Europe and Japan. Maxamine is being investigated in a variety of hematologic malignancies and solid tumors. For more details on Maxamine, see FO, p 395.

IL-2 Monotherapy

IL-2, as a single agent, is associated with results similar to those seen with prolonged post-remission therapy and may have a role in prolonging duration of complete remission in adult patients with AML who are in their first complete remission. In this study, 18 patients with AML were treated with IL-2 (4.5 x 10^5 U/m^2) daily by continuous infusion within three months of achieving CR, plus by bolus injection of IL-2 (1 x 10^6 U/m^2) on day 8 and weekly thereafter while continuing the continuous infusion. No further chemotherapy was administered after starting IL-2. Median CR duration was 53 weeks, with six patients alive in CR at a median follow-up time of 275 weeks. Seven patients continue in CR. To assess the significance of these results, two historical control patients receiving long-term post-remission therapy were randomly selected for each IL-2 patient. Outcome was the same in the two historical groups consisting of 18 patients each, suggesting validity of the matching procedure. In a comparison of the 36 controls with the 18 patients treated with IL-2 at four years, 14% (5/36) of controls and 33% (6/18) in the IL-2 group

were alive in CR as well as 19% (7/36) of controls and 39% (7/18) of those on IL-2 (Cortes J, etal, ASH97, Abs. 2252:505a).

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Shortened, Intensified Chemotherapy

Shortened, intensified chemotherapy has proven to be very encouraging in the treatment of acute lymphoblastic leukemia (ALL), particularly in patients with B lineage/Ph- disease. To reach this conclusion, 62 patients with ALL were treated with an initial course of therapy (DVPAsp), including doxorubicin (60 mg/m^2) on days 1-3, vincristine (1.4 mg/m^2) on days 1, 8, 15, 22, prednisone (60 mg/m^2) on days 1-28, and asparaginase (6000 U/m^2) on days 17-28. The second course of therapy (HdAC/Etopo) included ara-C (2000 mg/m^2) on days 1-4 and etoposide (500 mg/m^2) on days 1-4. The third course (HDMTX/MP) consisted of methotrexate (2380 mg/m^2) over 36 hours on days 1 and 15 and 6-mercaptopurine (75 mg/m^2) on days 1-28. The entire sequence was repeated once. Maintenance therapy with 6-mercaptopurine and methotrexate until 30 months continuing CR (CCR) followed the six courses of IV treatment.

Overall, 92% of patients treated (57/63) achieved a CR, with five non-responders (NR). Four patients withdrew, two died in CR, and 22 relapsed, leaving 29 patients (47%) in CCR. With a median follow-up of 2.5 years (0,1-9.7), five year disease-free survival (DFS) for all remission patients is 47%. In this group of patients, 86% of treated T-cell patients (12/14) achieved CR, with one withdrawing and two dying in CR. Their five-year DFS rate is 30%. While five of six Ph+ patients achieved CR, all relapsed within one year. In contrast, 35 of 36 patients with B lineage/Ph-disease achieved CR. In this group 23 remain CCR. With a median follow-up of 2.5 years, their 5 year DFS is 69% (Linker CA, etal, ASH97, Abs. 1485:333a).

ACUTE PROMYELOCYTIC LEUKEMIA (APL)

Concurrent Induction Chemotherapy and All-trans Retinoic Acid (ATRA)

The combination of all-trans retinoic acid (ATRA, Vesanoid; Roche) administered concurrently with induction chemotherapy has been shown to improve outcome of patients with acute promyelocytic leukemia (APL) when the white blood cells (WBC) count is <10 x 10^9/l, but does not improve outcome for those with WBCs >10 x 10^9/l who are at a high risk of early death. In this clinical trial (UK MRC ATRA), a short five-day pre-induction course of ATRA was compared to an extended course starting at the same time as chemotherapy and continuing until remission was achieved or a maximum of 60 days. The dose of ATRA was 45 mg/m^2/day. Induction therapy included doxorubicin or mitoxantrone (Novantrone; Immunex) with conventional doses of ara-C with thioguanine or etoposide as a third drug. Over a four year period, 239 patients with APL were randomized to short (119) or extended (120) ATRA.

The CR rate was superior in the extended arm, being 87% versus 69% in the short regimen, and this was evidenced by significant reductions in early death and resistant disease, as well as reduced risk of relapse, all of which translated into significantly better survival. At three years from entry in the study, survival rate on the short regimen was 53% compared to 74% in the extended arm. In actuality, the 72% (178) of patients who presented with WBC <10 x 109/l derived the most benefit. The CR rate was 94% on the extended ATRA treatment versus 76% in the short ATRA regimen and the three-year survival rate were 85% versus 60%, respectively (Burnett AK, etal, ASH97, Abs. 1474:330a).

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Cladribine

Cladribine (2-chlorodeoxyadenosine or 2-CdA, Leustatin; Ortho Biotech), the treatment of choice for hairy cell leukemia (HCL), was also found to be effective in untreated B-cell chronic lymphocytic leukemia (CLL). In a multicenter phase II clinical trial, conducted between February 1995 and December 1996, 54 patients with active disease (Rai Stage I disease=15, Stage II=18, Stage III=11, Stage IV=10) were treated with a daily two-hour IV bolus infusion of cladribine (0.14 mg/kg), for five consecutive days, every 28 days. If CR was reached after three cycles, no further treatment was administered and, if not, an additional three cycles were administered; median number of cycles was five.

At 17 months median follow-up, there were 14/54 CR (26%) (among them 1 with Stage III and 2 with Stage IV disease), 30/54 PR (56%) (among them 7 with Stage III and 5 with Stage IV disease), and disease stabilized in 1/54 (6%). Nine non-responders included 7 whose disease progressed, one who died early and one who was not treated according to protocol. Grade 3or 4 hematologic toxicities occurred in over half of the patients and autoimmune toxicities in 4. Grade 3 or 4 extramedullary toxicities included fever (n=14), rash (n=9), herpes zoster (n=6), pneumonia (n=7), and sinusitis (n=2). Other side effects included fatigue, diarrhea, and nausea (Tallman MS, etal, ASH97, Abs. 2574:578a).

Cladribine is also being investigated in a phase III clinical trial in Europe in ALL and in a phase I clinical trial (protocol ID: NCI-95-C-0092), being conducted by the Radiation Oncology Branch (Bethesda, MD) of the NIH, in the treatment of high-grade malignant glioma. In this clinical trial Cladribine is administered as a continuous-infusion in conjunction with accelerated, hyperfractionated, external-beam cranial irradiation.

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Decitabine

Decitabine, a novel hypomethylating agent under development by Pharmachemie (Haarlem, The Netherlands), shows encouraging results in the treatment of patients with chronic myelogenous leukemia (CML), particularly of CML in transformation. Hypermethylation of DNA or its specific sites is characteristic of tumor progression or resistance. Hypermethylation of the c-abl pro-

moter is associated with 40% to 50% of CML cases in the chronic phase and with 75% of CML cases in transformation. Decitabine, that has already shown activity in AML and myelodysplastic syndrome (MDS), was evaluated in 66 patients with CML in the accelerated (CML-AP=30) or blastic phase (CML-BP=36) who were treated with decreasing doses of decitabine. The first 13 patients were treated with an initial dose of 100 mg/m^2, administered over six hours, every 12 hours x 10 (1000 mg/m^2/course). Then the dose was reduced to 75 mg/m^2 in the next 22 patients, and to 50 mg/m^2 in the last 31 patients.

An objective response was seen in 46% (6/13) of patients at 100 mg/m^2, 55% (12/22) at 75 mg/m^2, and 39% (12/31) at 50 mg/m^2. A cytogenic response was noted in 3 patients (CML-BP=1, CML-AP=2). In the CML-BP patients, median response duration was 25 weeks and median overall survival was 26 weeks, with 22% remaining alive at one year. In those with CML-AP, median duration of response was 19 weeks and median overall survival was 58 weeks, with 35% remaining alive at two years. The most significant side effect was prolonged myelosuppression, with febrile episodes occurring in 53% of induction courses. A clinical evaluation of lower doses of decitabine in combination with topoisomerase I or II inhibitors is warranted (Kantarjian H, etal, ASH97, Abs. 352:81a).

MYELODYSPLASTIC SYNDROME (MDS)

Topotecan

Topotecan (Hycamtin; SmithKline Beecham), a potent topoisomerase I inhibitor, showed encouraging activity as monotherapy in MDS and chronic myelomonocytic leukemia (CMML), resulting in 30% CR. In order to improve this outcome, topotecan was used in combination with cytosine arabinoside (ara-C, Cytoxan; Bristol-Myers Squibb) in a phase II, single-institution, open-label study involving 35 patients, 21 with untreated MDS and 14 with untreated CMML. Treatment consisted of topotecan (1.25 mg/m^2) administered as a daily continuous 24-hour IV infusion, for five days, and high dose ara-C (1 g/m^2) administered as a daily two-hour infusion, also for five days. Patients were also treated prophylactically with antibiotics (ciprofloxacin, fluconazole, and acyclovir) and those over 50 years-of-age were offered induction therapy in a protected environment with 19 of 27 (70.4%) eligible patients accepting this option.

At a median six-month follow-up, 63% (22/35) of those treated achieved CR [43% (6/14) with CMML and 76% (16/21) with MDS], with 80% of them doing so after only one treatment course. Also, those in CR no longer required blood transfusions and their pre-existing chromosomal abnormalities disappeared. Topotecan was generally well-tolerated, with major side effects being fever in 59% of induction courses and neutropenia with 48% documented infections. Severe mucositis and gastrointestinal problems occurred in only 3% of patients.

Investigators also compared these results with those from another study in which 55 patients with MDS were treated with a combination regimen (FAI-G ATRA) consisting of fludarabine (Fludara; Berlex), ara-C, idarubicin (Idamycin; Pharmacia & Upjohn) with or without granulocyte-colony stimulating factor (G-CSF) and all-trans retinoic acid. Preliminary analysis showed that FAI-G ATRA-treated patients only achieved a CR rate of 40%, compared to the 63% rate seen with the topotecan/ara-C combination (Beran M, etal, ASH97, Abs. 2593:583a).

Amifostine in Combination Therapy

The combination of pentoxifylline (Trental; Hoechst Marion Roussel), ciprofloxacin (Cipro; Bayer), and dexamethasone (PCD), with the addition of the cytoprotective amifostine (Ethyol; Alza), has proven to be highly active in improving ineffective hematopoiesis in patients with MDS. Because PCD therapy had previously shown positive results in approximately 40% of patients treated and amifostine had also demonstrated efficacy in MDS, a study was carried out to evaluate safety and efficacy of combining these two approaches in patients with MDS. All patients were treated with continuous therapy with PO pentoxifylline (800 mg), three times a day, and PO ciprofloxacin (500 mg) twice daily. Amifostine was administered IV, thrice weekly, at three dose levels (200 mg/m^2, 300 mg/m^2 and 400 mg/m^2) to 10 patients at each dose level. Response was evaluated after 12 weeks of therapy. At that time non-responders were also treated with daily PO dexamethasone (4.0 mg) for four weeks and responders continued with the usual treatment for 12 more weeks, at which time amifostine administration was reduced to a once weekly regimen.

Of the 28 patients enrolled in the study, 17 were being treated at the time of this report, with 11 being evaluable as to efficacy and safety. Among those evaluable who were treated for at least 12 weeks, 6 either had refractory anemia (RA) or RA with ringed sideroblasts (RARS) with the remaining 5 having A with excess blasts (RAEB) or RAEB in transformation (RAEB-t). Hematopoietic responses were noted in 8 (RA/RARS=4 and RAEB/RAEB-t=4) of 11 patients (73%). Transfusion requirements in responders, either in the form of platelets and/or red blood cells, was reduced by at least 50%. Of those responding, 4 did so based on the original PCD plus amifostine regimen, while the other 4 responded after addition of dexamethasone. Among responders, six were treated with 200 mg/m^2 of amifostine and two with 300 g/m^2; it was too early to evaluate those being treated with 400 mg/m^2 (Raza A, etal, ASH97, Abs. 367:84a).

LYMPHOMAS

Poor Prognosis Malignant Lymphoma

Intensive chemotherapy in combination with granulocyte macrophage-colony stimulating factor (GM-CSF) appears to be a safe and effective treatment alternative in patients with poor prognosis malignant lymphoma who are rarely cured by conventional chemotherapy. For this reason, efficacy and safety of an intensified regimen was evaluated in 60 newly diagnosed patients with high risk malig-

nant lymphoma with 42 having bulky disease. The regimen consisted of IV cyclophosphamide (1 g/m^2), epirubicin (120 mg/m^2) and vincristine (2 mg) on day 1, daily PO prednisone (100 mg), on days 1-5, and IV bleomycin (10 mg/m^2) on day 14. Daily administration of GM-CSF (mg/kg) to relieve severe immunosuppression was started on day 4 and lasted for 10 days. All patients were treated with six cycles of therapy administered every 21 days. Within a median follow-up period of 36 months, among the 80% (48/60) of patients who experienced CR, only 3 relapsed while 75% (45/60) remained alive, free of disease. There were 20 episodes of Grade 4 granulocytopenia in 360 cycles of chemotherapy. There were no deaths related to therapy and cardiac function has remained normal in all patients (Aviles A, etal, ASH97, Abs. 841:190a).

Non-Hodgkin's Lymphoma (NHL)

The outlook of patients with advanced B-cell NHL is improving thanks to several novel treatments. One such approach that uses a monoclonal antibody (MAb) that depletes B cells by binding to a protein (CD20 antigen) found on the surface of mature B cells and B-cell tumors, developed by IDEC Pharmaceuticals, was launched by Genentech (South San Francisco, CA) in the USA in December 1997. Two other treatments, both involving radioimmunotherapies based on MAb targeting of B cells are in late stages of development. First in line is ^{131}Iodine (^{131}I) anti-B1 antibody conjugate (Bexxar) being developed by Coulter Pharmaceuticals (Palo Alto, CA).

Bexxar has entered phase III clinical trials based on results of a phase II, multicenter, single-arm, open-label trial that was designed to ascertain safety and efficacy of Bexxar in 45 patients with low-grade (34) and transformed low-grade (11) B-cell NHL, all of whom had failed prior chemotherapeutic regimens within the past year. Patients were first administered unlabeled anti-B1 MAb to prevent uptake of radiolabeled MAb by healthy organs and then were administered a dosimetric dose of Bexxar (5 mCi) to calculate radioactive clearance in each patient. Based on this information, a patient-specific dose of Bexxar was arrived at based on platelet count, so that a total body dose of 65 centigray (cGy) was delivered to those with 100,000 to 149,999 platelets/mm (n=9) and 75 cGy to those with platelet counts over 150,000 platelets/mm^3 (n=36). Patients were assessed at six weeks, 12 weeks, and every 12 weeks thereafter, for two years.

Overall response rate was 60% (27/45), comprised of 31% CR (14/45) and 29% (PR) (13/45). Stable disease was reported in 33% (15/45) and disease progressed in the remaining 7% (3/45) of patients. Median duration of CR at the time of this report was 13.6 months, with an actual median duration not having been reached because 10 of 14 patients (71.4%) remained in CR (Kaminski MS, etal, ASH97, Abs. 2268:509a). IDEC is also developing a radioimmunoconjugate (IDEC Y2B8) using yttrium as the radioisotope that showed very high response rates in phase I/II clinical trials.

MULTIPLE MYELOMA

Interferon-α Maintenance

Mephalan (Alkeran; Glaxo Wellcome) and prednisolone (MP) followed by interferon (IFN)-α plus dexamethasone (DEX) maintenance therapy proved to be less toxic and superior in disease stabilization than an intensified experimental induction treatment of six alternating courses of intermediate-dose cyclophosphamide; DEX, Adriamycin, and vincristine (DAV); and cisplatin, etoposide, and DEX (CED).

Between October 1990 and December 1994, 390 patients were randomized to either MP or the intensified regimen. Patients resistant or relapsing from one arm shifted to the other. In this group, 207 patients who responded to treatment were placed on maintenance therapy, being randomized to either IFN or IFN plus DEX until relapse. IFN was administered at a dose of 3 mega units thrice weekly and DEX (40 mg) for four days every month for 12 courses, then every two months. At a median follow-up of 51 months, MST was 43 months. The intensified regimen induced Grade 4 hematologic toxicity in 25% of patients versus 7% in the MP arm. Response to treatment was very similar in the two groups (52% versus 48%). Remission duration in responders, however, was significantly prolonged with MP and IFN plus DEX treatment, being 30 months on MP plus IFN plus DEX, 23 months on MP plus IFN, 22 months on intensified treatment plus IFN plus DEX, and 15 months intensified treatment plus IFN (Boccadoro M, etal, ASH97, Abs. 1586:355a).

In a similar study, conducted between 1992 and 1996, a limited primary therapy of daily oral melphalan (8 mg/m^2) for four days and oral DEX (20 mg/m^2) on days 1-4, 9-12, 17-20, was administered to 154 consecutive patients with low, or intermediate-grade multiple myeloma. The response rate, defined as >75% reduction of myeloma protein production and <5% marrow plasma cells, was 55% and was reached at a maximum of 3 courses of therapy. Within 5 months, all 85 responders were randomized to maintenance treatment either using IFN-α-2b (3 MU) or DEX. Subsequent median time to relapse was 15 months and 11 months, respectively. MST of randomized patients on either treatment group was approximately four years (Alexanian R, ASH97, Abs. 1585:355a).

Clarithromycin

Use of clarithromycin (Biaxin; Abbott) as primary treatment for active multiple myeloma is based upon positive results with this treatment in MALT lymphoma with t(11:14)(q12:q32)-associated *Helicobacter pylori* infection, and the fact a circulating nucleotide sequence which contains the same Bcl-1/JH 5/6 breakpoint region, was detected in patients with active multiple myeloma. Thirty patients were placed on a basic schedule of *bid* clarithromycin (500 mg) with the longest follow-up being one year. There were 6 CR (greater than 75% regression) and 7 PR (greater than 50% regression); 6 patients experienced stable disease, 4 had a mixed response, and 7 were too early to evaluate. The first patient to be treated, who was

previously untreated, was in full clinical remission at approximately one year follow-up. Dramatic responses occurred in two patients who had relapsed after stem cell transplant and in one patient refractory to both VAD and melphalan. As of the time of this presentation, patients with IgA and IgG, k sub type, were best responders compared with λ BJ and non-secretory patients in whom efficacy has been lower (Durie BGM, etal, ASH97, Abs. 2578:57a).

TREATMENT OF CHEMOTHERAPY-INDUCED SIDE EFFECTS

Thrombocytopenia

Pegylated recombinant human mega-karyocyte growth and development factor (PEG-rHuMGDF), a new platelet growth factor under development by Amgen which helps protect against low platelet counts, was well tolerated, safe, and highly effective, increasing circulating platelets more than fourfold in 10 to 15 days. In a randomized, placebo-controlled, blinded, cross-over, sequential, dose-escalation study, 59 healthy donors (18-50 years) were treated either with placebo, or PEG-rHuMGDF (1 mg/kg or 3mg/kg), injected SC on day one only in each of two consecutive 28 day periods. Platelet counts were measured on days one, six, nine, 12 and 15 pre-and post-apheresis, and on day 22, with total platelet yield assessed. Donors were apheresed to 85% of total blood volume. Platelets then were assigned to recipients on a first in-first out basis. Platelet counts were measured pre- and 18 to 24 hours post-transfusion, and an absolute increment (AI) (post-transfusion platelet count minus pre-transfusion platelet count) was calculated.

Overall, 110 of 115 apheresis procedures were completed in the 59 donors. Of the 110 apheresis products, 90 (85%) were transfused. In the donor groups, in 65 placebo apheresis procedures, median platelet yield was 3.7×10^{11}, while in 23 PEG-rHuMGDF 1 m/kg procedures it was 5.6×10^{11}, and in 22 PEG-rHuMGDF 3 mg/kg procedures it was 11×10^{11}. Increased total platelet yields in the donors were associated with larger AIs in the recipients, going from 11 x 10^9/l in the placebo group to 43.5 x 10^9/l in the PEG-rHuMGDF 3 mg/kg group (Kuter D, etal, ASH97, Abs. 2579:579a).

Mucositis

Recombinant keratinocyte growth factor (rHuKGF), a recombinant form of the naturally occurring growth factor that stimulates growth of cells that make up the membrane lining the surface of the gastrointestinal (GI) tract, under development by Amgen, may be potentially effective in treatment-related mucositis. Mucositis is becoming more common because of increased use of high-dose chemotherapy protocols and multimodality approaches incorporating radiation therapy. Better control of other serious chemotherapy-related complications has allowed increasingly aggressive treatment regimens giving rise to less life-threatening side effects such as mucositis which, nevertheless may limit, interrupt, or stop therapy when development of severe oral and GI lesions ensues.

In a phase I clinical trial to examine safety, tolerability, pharmacokinetics, and biological activity of rHuKGF, 61 healthy volunteers (26 males and 35 females), were treated either with placebo or rHuGKF at daily doses of 0.2, 1.0, 5.0, 10, and 20 mg/kg, administered either as a single IV dose (3 patients per cohort on rHuGKF and one on placebo) or as a daily IV injection for three consecutive days (6 patients per cohort on rHuGKF and two on placebo). Extensive routine and special tests and procedures were performed at baseline and at selected times after first dosing. Studies were initially carried out in healthy volunteers because of the possibility of causing infection in immunosuppressed cancer patients.

Results showed that rHuGKF was safe and well tolerated, with no severe, serious or clinically significant effects observed when administered up to 20 mg/kg daily for three days. Biologic activity was confirmed in buccal mucosa, showing a statistically significant dose-response effect. This data is being used as a starting point, with programs already in place to evaluate safety and efficacy of rHuGF in patients at risk for mucositis, such as those with head and neck cancer, advanced colorectal cancer, or on high-dose chemotherapy with stem cell transplantation for lymphoma. Results are expected in 1998 (Serdar CM, etal, ASH97, Abs. 761:172a).

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