FUTURE ONCOLOGY

TECHNOLOGY, PRODUCTS, MARKETS AND SERVICE OPPORTUNITIES

A NEW MEDICINE PUBLICATION AUGUST 31, 2003 VOLUME 7, NUMBER 6/7

MEETING COVERAGE

RANDOMIZED CLINICAL TRIALS WITH NOVEL ANTICANCER AGENTS — FROM THE 2003 MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

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After many years of development, over 70 novel agents have entered phase III clinical trials for at least one cancer indication (Exhibit 1). Generally, in most cases, the novel agent is being evaluated in combination with established treatments, but several drugs have reached phase III clinical trial status also as monotherapies. Despite all this activity, however, the anticancer effects of many of these agents have been marginal with none offering the possibility of a cure.

INCREASED EMPHASIS IN ALL ASPECTS OF CLINICAL TRIALS IN ONCOLOGY

There is an ongoing effort to improve all aspects of clinical trials in oncology. There are many issues plaguing development of meaningful clinical trial designs that simultaneously benefit the patient and advance the state-of-the-art in the development of anticancer drugs. As carried out today, the clinical testing of cancer drugs is a chaotic process that compromises patient care and, despite great expense and effort, produces little in terms of fundamentally improving the treatment of this disease.

Currently, major efforts are being undertaken to institute basic changes in the way clinical trials of anticancer agents are conducted in the USA. These changes are being put into motion not only to remove some of the most egregious lapses in the system, but also to streamline the process to benefit both patients and drug developers alike.

Efforts to Increase Patient Participation

There is an ongoing effort to increase patient participation in early-stage clinical trials. Currently, only about

3% to 4% of adults newly diagnosed with cancer enter phase I or phase II clinical trials.

In July 2002, the National Cancer Institute (NCI) unveiled a plan to spend $3 million over the next two years to increase participation of cancer patients in early-stage clinical trials. Several drug companies, including Aventis, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline and Novartis, contributed a total of $5.7 million to the effort. This new initiative will fund five to eight studies to develop approaches to educate patients about the importance of clinical trials, and to improve the public's trust in the institutions conducting such trials.

Proposed methodologies include development of an online protocol information system with culturally relevant literature, and budgeting allowances for travel and day care for prospective trial enrollees. Grant award emphasis was also placed on the accessibility of these programs to as many people as possible.

Institutions receiving funding include Massachusetts General Hospital (Boston, MA), University of Colorado Health Sciences Center (Denver, CO), Washington University (St. Louis, MO), University of Pittsburgh Cancer Institute, University of California Davis Cancer Center, and Ohio State University Comprehensive Cancer Center (Columbus, OH). The project was put together with the cooperation of Friends of Cancer Research (Washington, DC), a nonprofit organization that mobilizes public support for cancer research funding, and provides public education on key public policy issues, the Foundation for NIH that builds and fosters collaborative relationships with philanthropy, industry, and academia to improve health through scientific discovery, as well as the NCI and the Association of American Cancer Institutes (AACI).

Streamlining Cancer Drug Development

In May 2003, the NCI and the Food and Drug Administration (FDA), both part of the Department of Health and Human Services (HHS), announced a joint program to streamline anticancer drug development. The two agencies will share knowledge and resources to facilitate the development of new anticancer drugs, and speed their delivery to patients. This multipart interagency agreement is being established to create a more unified, integrated, and efficient approach in order to enhance the efficiency of clinical research, and the scientific evaluation of new cancer treatments. The collaboration will take full advantage of the combined knowledge of the two agencies base to ensure proper attention to the many new kinds of anticancer agents in the pipeline. Molecularly targeted drugs, and other novel agents that offer great promise, also present new challenges that require more collaboration between those involved in their discovery and development.

An NCI/FDA Oncology Task Force consisting of senior staff from both agencies, will oversee implementation of the specific components of this agreement. Areas of collaboration include:

- Development and standardization of markers of clinical significance that would serve as surrogate endpoints to speed the evaluation of new drugs; biomarkers will be identified that demonstrate a drug's clinical effectiveness and/or potentially serve as a surrogate endpoint, substituting for more conventional measures, such as survival time or mortality
- Creation of a cancer bioinformatics infrastructure to improve data collection, integration, and analysis for preclinical, preapproval, and post-approval research across all of the sectors involved in the development and delivery of cancer therapies
- Collaboration on clinical proteomics (involving the discovery of protein markers in the blood that can be used to detect and monitor disease course and drug response) as a possible model for initiatives in areas such as diagnostic imaging and molecular targeting
- Advancement of the development and evaluation process for cancer chemoprevention agents, including the development of clinically meaningful endpoints
- Systematic review of current policies to identify other ways in which FDA and NCI collaborations can enhance the development and regulatory process for cancer-related technologies
- Alerting consumers of the consequences of lifestyle choices, diet and nutrition, as they pertain to cancer prevention

Reporting and Registering Clinical Trials

The purpose of a clinical trial is to determine the anticancer activity of a certain regimen in a selected patient population. Unfortunately, there are no rules as to when and how results of clinical trials are reported in the literature. First of all, there is no requirement that results of a clinical trial are reported at all. Therefore, as expected, investigators do not routinely publish such information in any outlet. Additionally, when negative results are reported, they are in abstract form at a meeting rather as a complete presentation in a peer-reviewed journal. This is unfortunate because more is learned by the numerous failures in this area rather than the few successes.

The fact that it is not possible to find information about all initiated clinical trials has become an international concern. The fact that trials with positive findings are more often published than those with negative findings (publication bias) is doubly worrisome. The creation of a comprehensive international register of initiated clinical trials, with each trial assigned a unique identifier, is being suggested to inform reviewers, physicians, and consumers/patients about new, ongoing and completed trials. Such a registry would also address the problem of publication bias, allowing interested parties to directly contact the investigators involved in unreported trials. A comprehensive registry would also allow clinicians to be better informed

Exhibit 1
Novel Anticancer Agents in Ongoing or Recently Completed Single-agent or Combination, Randomized, Phase III Clinical Trials*

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Development Status ❑ Indications
Abbott Laboratories	Atrasentan ❑ ABT-627 (formerly A-147627)	Orally bioavailable endothelin A (ETA) receptor (ETAr) antagonist ❑ PO	Phase III (begin 11/01, ongoing 6/03)➢USA ❑ nonmetastatic, hormone-refractory prostate cancer (HRPC); phase III (begin 11/02, ongoing 6/03)➢USA ❑ HRPC
Access Oncology ❑ Pennsylvania State U	O(6)-benzylguanine (BG) ❑ O6BG, O6-BG ❑ Alkylade	Suicide substrate inactivator for O(6)-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein that may be important in tumor resistance to alkylating agents ❑ infusion	Phase III (begin 12/02, ongoing 6/03)➢USA (combination) ❑ newly diagnosed glioblastoma multiforme (GBM) or gliosarcoma
Aeterna Laboratories ❑ Grupo Ferrer Internacional, Medac	[AElig]-941, AE-941 ❑ Neovastat	Novel antiangiogenic shark cartilage liquid extract; inhibits matrix metalloproteinases (MMP) and interacts with vascular epithelial growth factor receptor (VEGFr) ❑ PO	Phase III (begin 3/00, ongoing 6/03) ➢USA, Canada (combination) ❑ locally recurrent non-small-cell lung cancer (nsclc); phase III (begin 5/00, closed 12/01)➢USA, Canada, Europe ❑ refractory renal cell carcinoma (RCC)
Alfacell ❑ Scientific Protein Laboratories	Ranpirnase (formerly P-30 protein) ❑ Onconase	Cytotoxic ribonuclease with antitumor properties; originally isolated from the ova and early embryos of the Northern leopard frog (Rana pipiens), it was identified by amino acid sequencing to be a small single-chain protein composed of 104 amino acid residues; has a high degree of homology with the digestive enzyme pancreatic ribonuclease A ❑ IV	Phase III (begin 5/97, ongoing 6/03)➢USA, Europe (Germany, Italy) ❑ unresectable, advanced or recurrent malignant mesothelioma; phase III (completed 1/99)➢USA ❑ pancreatic cancer
Allos Therapeutics ❑ National Cancer Institute (NCI)	Efaproxiral sodium ❑ RSR13	Synthetic allosteric hemoglobin modifier that increases the release of oxygen from hemoglobin ❑ continuous IV with central venous access	NDA (begin 6/03)➢USA ❑ breast cancer with brain metastases; phase III (begin 2/00, completed 8/02) ➢USA, Canada, Europe, Australia (multimodality) ❑ solid tumors metastasized to the brain; phase III (planned 06)➢USA, Canada ❑ locally advanced, unresectable, Stage IIIa or IIIb nsclc
AltaRex ❑ Biomira, United Therapeutics, Medison Pharma, Dompe Farmaceutici, Abbott Laboratories	Oregovomab ❑ B43.13 ❑ OvaRex	Murine monoclonal antibody (MAb) that binds with high affinity to CA125 tumor-associated antigen (TAA) and modulates immunity by complex formation with circulating CA125; these immune complexes are then taken up by antigen-presenting cells, and are preferentially processed and presented to T cells ❑ IV	Phase III (begin 12/02, ongoing 6/03)➢USA ❑ advanced ovarian cancer
American BioScience ❑ American Pharmaceutical Partners	Paclitaxel ❑ ABI-007	Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel ❑ IV, intra-arterial	Phase III (completed 12/02)➢USA, Europe ❑ metastatic (Stage IV) breast cancer
Amgen ❑ ImClone Systems	Flt-3 ligand (Flt-3L), Flt3L ❑ Mobist	Stem cell growth factor, consisting of cloned cDNA encoding a ligand for the Flt-3 receptor, in development to mobilize stem cells into the peripheral circulation ❑ injection	Phase III (begin 8/00, completed 10/02)➢USA ❑ acute myeloid leukemia (AML) in CR

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Antigenics ❑ Fordham U, Perseptive BioSystems, Sigma-Tau, Mount Sinai School of Medicine, Medison Pharma	HSPPC-96 ❑ Oncophage	Individualized heat-shock protein (hsp) cancer vaccine that elicits an immune response without requiring adjuvants ❑ IV, intradermal, *ex vivo*	Phase III (begin 6/00, ongoing 6/03) ➢USA, Europe ❑ locally advanced RCC; phase III (begin 3/03)➢Europe (Italy, Poland, Sweden, UK), USA (combination) ❑ metastatic malignant melanoma
Antisoma ❑ Imperial Cancer Research Fund (ICRF), U California, Cancer Therapeutics, BioInvent International, Roche	Pemtumomab ❑ R1549 ❑ Theragyn	Yttrium-90-labeled murine IgG1 MAb HMFG1 recognizing polymorphic epithelial mucin (PEM) ❑ intraperitoneal (IP)	Phase III (begin 98, ongoing 6/03)➢USA, Europe, Australia ❑ ovarian cancer
Aphton ❑ U Nottingham, Aventis Pasteur	Anti-gastrin-17 (G17DT) ❑ Gastrimmune	Oil-based vehicle incorporating a synthetic peptide fragment of hormone G17 which is targeted to be neutralized, a carrier (diphtheria toxoid) conjugated to synthetic peptides, and an adjuvant ❑ intramuscular (IM)	Phase III (begin 4/00, ongoing 6/03) USA (combination), phase III (begin 2/01, completed 3/03)➢USA, Europe (combination) ❑ metastatic pancreatic cancer
BioMedicines ❑ Schering	Atamestane ❑ Biomed 777	Aromatase inhibitor; oral estrogen synthesis blocker ❑ PO	Phase III (begin 8/02, ongoing 6/03)➢USA, Canada, Europe (Russia, Ukraine) ❑ metastatic or locally advanced breast cancer, first line
Biomira ❑ Corixa, Biomembrane Institute, Merck KGaA	Theratope STn-KLH	Synthetic cancer-associated carbohydrate antigen analog of Sialyl Tn (STn) [NANAa (2-6) Gal NAc], attached to keyhole limpet hemocyanin (KLH) protein carrier, mixed with Detox-B SE (Enhanzyn) adjuvant ❑ injection	Phase III (begin 11/98, closed 3/01)➢USA, Canada, Europe, Australia, New Zealand ❑ metastatic or recurrent breast cancer
BioNumerik Pharmaceuticals ❑ Grelan Pharmaceutical, Baxter Oncology	Dimesna ❑ BNP7787	Water-soluble, reducible disulfide acting as a thiol-modulating chemoprotectant for cytotoxic chemotherapy, including taxanes and platinum-based anticancer drugs ❑ PO, IV	Phase III (ongoing 6/03)➢USA (combination) ❑ paclitaxel-related neurotoxicity
Boehringer Ingelheim ❑ Yale U, Vion Pharmaceuticals	Porfiromycin, Porphiromycin ❑ NSC 56410 ❑ Promycin	Bioreductive alkylating agent ❑ IV	Phase III (begin 12/97, completed 1/01)➢USA, phase III (begin 4/98, ongoing 6/03)➢Europe (UK) ❑ advanced head and neck cancer
Bristol-Myers Squibb ❑ Celltech Group	BMS-275291, D-2163	Matrix metaloproteinase inhibitor (MMPI) that acts selectively against specific MMP enzymes without affecting TNF or IL-1 release believed to play a key role in the inflammation process and may lead to side effects ❑ PO	Phase II/III (begin 4/00, ongoing 6/03)➢Europe (UK), USA (combination) ❑ advanced or metastatic nsclc
Cancervax ❑ John Wayne Cancer Institute	Canvaxin	Allogeneic, polyvalent whole-cell vaccine expressing multiple antigens (n=38) that induce both a cellular (T cell) and humoral immune response.	Phase III (begin 3/98, temporary closed 1/03)➢USA, Europe (France, Italy, UK), Australia, Israel ❑ resected, metastatic (Stage IV) malignant melanoma; phase III (begin 2/00, temporary closed 1/03)➢USA, Europe (France, Italy), Australia, Israel ❑ resected, advanced (Stage III) malignant melanoma
CBA Pharma	CBT-1	Natural product, multidrug resistance (MDR) modulator ❑ PO	Phase III (ongoing 6/03)➢USA ❑ advanced or metastatic nsclc, first line

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Celgene ❑ Cornell U, EntreMed, Children's Hospital Boston, National Institutes of Health (NIH)	CDC501, CDC-501, CDC-5013, CC5013, CC-5013 ❑ Revimid	Small molecule compound, a member of immunomodulatory drugs (IMiD) that are structurally and mechanistically similar to thalidomide ❑ PO	Phase III (begin 1/03)➢USA, Canada ❑ refractory or recurrent multiple myeloma; phase III (begin 10/02, ongoing 6/03)➢Europe (UK, Estonia, Germany, Latvia, Lithuania, Ukraine), South Africa, Australia, phase II/III (begin 4/03)➢USA ❑ metastatic malignant melanoma
Cell Therapeutics ❑ U Texas M. D. Anderson Cancer Center, PG-TXL, Chugai Pharmaceutical, Natural Pharmaceuticals, US Oncology	Paclitaxel ❑ CT-2103 ❑ Xyotax (previously PG-TXL)	Poly(L-glutamic acid)-paclitaxel conjugate with enhanced water solubility compared to unconjugated paclitaxel ❑ IV	Phase III (begin 1/03)➢USA, Canada, phase III (begin 1/03)➢USA, phase III (begin 1/03)➢USA (combination) ❑ advanced (Stage IIIb or IV), or recurrent nsclc; phase III (begin 6/02) ➢USA (combination) ❑ refractory or recurrent ovarian cancer or peritoneal cancer, or primary advanced or metastatic (Stage III or Stage IV) ovarian cancer, first line
Daiichi Pharmaceutical	Exatecan mesylate ❑ DX-8951f	Synthetic, water-soluble camptothecin analog; exhibits more potent and broader antitumor activity than other topoisomerase I inhibitors ❑ IV	Phase III (begin 9/01, closed 1/03) ➢USA, Canada (combination) ❑ locally advanced or metastatic ovarian cancer, first line
Dendreon ❑ Immune Response, Mayo Clinic, Kirin, U Brussels, Covance Biotechnology Services	APC8015 ❑ Provenge	Cellular product consisting of autologous peripheral blood mononuclear cells (PBMC) enriched for a dendritic cell fraction which is pulsed with a prostatic acid phosphatase (PAP)-GM-CSF construct ❑ IV	Phase III (begin 1/00, completed 7/01)➢USA, phase III (begin 5/03) ➢USA ❑ advanced or metastatic HRPC; phase III (begin 6/01, ongoing 6/03)➢USA ❑ early-stage, hormone-sensitive prostate cancer
Eli Lilly ❑ Princeton U	Pemetrexed disodium ❑ LY 231514 ❑ Alimta	Multitargeted antifolate (MTA) that inhibits at least three enzymes (thymidylate synthase or TS, dihydrofolate reductase or DHFR, and glycinamide ribonucleotide formyltransferase or GARFT) involved in folate metabolism and DNA synthesis ❑ IV	Phase III (closed 01)➢USA, Europe (UK, Germany, France, Spain), Australia (combination) ❑ advanced or metastatic mesothelioma; phase III (begin 5/02, closed 3/03) ➢USA, Europe, Australia, Taiwan, South America (combination) ❑ pancreatic cancer; phase III (begin 3/01, completed 2/02)➢USA, Australia (combination) ❑ advanced or metastatic nsclc
Eli Lilly ❑ Chugai Lilly Clinical Research, Chugai Pharmaceutical	Zosuquidar trihydrochloride ❑ LY335979	Potent, selective, *in vitro* inhibitor of P-glycoprotein (P-gp) ❑ continuous IV	Phase III (begin 12/02, ongoing 6/03) ➢USA (combination) ❑ high-risk, refractory anemia with excess blasts (RAEB) in transformation, refractory RAEB anemia in transformation, first line
Eli Lilly	Arzoxifene ❑ SERM III, LY 353381	Analog of raloxifene; third generation selective estrogen receptor modulator (SERM) ❑ PO	Phase III (begin 01, completed 3/03) ➢USA, Argentina, Chile, India, Mexico ❑ locally advanced or metastatic breast cancer
Eximias Pharmaceutical ❑ Pfizer Global Research and Development	Nolatrexed dihydrochloride ❑ AG337 ❑ Thymitaq	Specific, membrane permeable, lipophilic, non-polyglutamated inhibitor of thymidylate synthase (TS); induces apoptosis ❑ continuous IV, PO, IP, IM	Phase III (begin 10/00, ongoing 6/03)➢USA, Canada, Europe, South Africa ❑ primary, inoperable liver cancer

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Genentech ❑ ImmunoGen	Bevacizumab ❑ rhuMAb-VEGF, NSC-704865 ❑ Avastin	Bevacizumab is a chimeric MAb antagonist of vascular endothelial growth factor (VEGF); angiogenesis inhibitor ❑ IV	Phase III (begin 10/00, completed 4/03)➢USA, South Africa (combination), phase III (begin 7/00, completed 10/02)➢USA (combination) ❑ metastatic colorectal cancer; phase III (begin 8/00, completed 12/01)➢USA (combination) ❑ locally recurrent or metastatic breast cancer; phase II/III (begin 7/01, ongoing 12/02)➢USA, South Africa (combination) ❑ advanced (Stage IIIb or Stage IV), or recurrent nsclc
Genetronics Biomedical ❑ Boehringer Ingelheim, Johnson & Johnson, U South Florida Research Foundation	Medpulser electroporation therapy	Electric field generator; induces pore formation on cell membranes to increase permeability of DNA delivery ❑ transdermal	Phase III (begin 5/02, ongoing 6/03) ➢USA ❑ recurrent or refractory squamous cell carcinoma of the head and neck
Genitope	GTOP-99	Customized (patient-specific) immunotherapy using recombinant idiotype conjugated to KLH with GM-CSF ❑ *ex vivo*, injection	Phase III (begin 11/00, ongoing 6/03) ➢USA, Canada (combination) ❑ follicular, Stage III/IV non-Hodgkin's lymphoma (NHL)
Genta ❑ Alliance Pharmaceutical, Avecia, U Pennsylvania, Aventis	Oblimersen sodium (formerly augmerosen) ❑ G3139 ❑ Genasense	An 18-mer fully phosphorothioated antisense oligonucleotide which targets the bcl-2 gene; the lead compound of the Anticode (antisense) technology platform ❑ SC, IV	Phase III (begin 7/00, closed 2/03) ➢USA, Canada, Europe, phase III (begin 10/02, ongoing 6/03) ➢USA ❑ metastatic malignant melanoma; phase III (begin 7/01, ongoing 6/03)➢USA (combination) ❑ relapsed or refractory chronic lymphocytic leukemia (CLL); phase III (begin 12/00, completed 1/03)➢USA (combination) ❑ relapsed or refractory multiple myeloma; phase II/III (begin 10/01, ongoing 6/03) ➢USA, Canada, Russia ❑ refractory nsclc
Ilex Oncology ❑ Aventis Pharma	Eflornithine, alpha difluoromethylornithine HCl (DFMO)	Specific, enzyme-activated, irreversible inhibitor of ornithine decarboxylase; inhibits growth of tumor cells and promotion and progression phases of carcinogenesis ❑ injection, PO	Phase III (completed 99)➢USA ❑ anaplastic glioma; phase III (begin 9/98, completed 9/02)➢USA ❑ nonmelanoma skin cancer; phase III (begin 4/00, completed 11/01) ➢USA ❑ low-grade, superficial bladder cancer
ImClone Systems ❑ Memorial Sloan-Kettering Cancer Center, Merck KGaA, Ludwig Institute for Cancer Research	Mitumomab ❑ EMD-60205 ❑ BEC2	Murine anti-idiotypic MAb, which mimics TAA, GD3 ganglioside, and stimulates a stronger immune response than natural GD3 ❑ IV, intradermal	Phase III (begin 9/98, completed 2/03)➢USA, Europe ❑ limited disease sclc
ImClone Systems ❑ U California San Diego, Aventis Pharma, Merck KGaA, Bristol-Myers Squibb, Impath	Cetuximab ❑ IMC-C225 ❑ Erbitux	Chimerized MAb directed against epidermal growth factor receptor (EGFr) ❑ IV	Phase III (begin 5/00, ongoing 9/01) ➢USA, Europe (multimodality), phase III (begin 6/99, closed 8/01) ➢USA (combination), phase III (begin 6/99, closed 6/01)➢USA ❑ advanced, refractory, head and neck cancer; phase III (begin 5/00, ongoing 6/03)➢USA (multimodality) ❑ advanced or metastatic cancer of the oropharynx
Immuno-Designed Molecules (IDM) ❑ Medarex	IDM-1 ❑ Osidem	Monocyte-derived Activated Killer (MAK) cells associated with a bispecific anti-HER2/neu MAb, previously in clinical development as MDX-210 ❑ injection	Phase III (ongoing 6/03)➢Europe, Australia, Canada ❑ advanced (Stage III) ovarian cancer

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Immunomedics ❑ Repligen, Amgen	Epratuzumab ❑ hLL2, hCD22, AMG 412 ❑ LymphoCide	Humanized MAb targeting the CD22 TAA ❑ injection	Phase III (begin 9/01, closed 1/03) ➢USA, Canada, Europe ❑ refractory, low-grade, or indolent NHL
Intracel ❑ Mentor	BCI-ImmuneActivator (formerly KLH-ImmuneActivator)	Proprietary formulation of KLH for intravesicular immunotherapy of bladder cancer ❑ intravesical	Phase III (begin 10/01, ongoing 6/03) ➢USA ❑ refractory carcinoma *in situ* (CIS) of the bladder
Introgen Therapeutics ❑ Oncormed, U Texas M. D. Anderson Cancer Center, Sidney Kimmel Cancer Center	Ad5CMV-p53, Ad-p53 ❑ RPR/INGN-201, RPR/INGN 201, INGN 201 ❑ Advexin	E1/E3-deleted, replication-defective adenoviral vector containing wild-type p53 cDNA under the control of a CMV promoter ❑ IV, IP, intralesional, intratumoral, intra-arterial, bronchial lavage, intravesical, intracranial, intracerebral	Phase III (begin 5/01, ongoing 6/03) ➢USA, Canada, Japan Europe (combination) ❑ refractory squamous cell carcinoma of the head and neck
Isis Pharmaceuticals ❑ Eli Lilly	LY900003 (formerly known as ISIS-3521, ISI641A, CGP64128A) ❑ Affinitac, Affinitak	20-mer antisense phosphorothioate antisense oligonucleotide inhibitor of protein kinase C (PKC)α isoform gene expression ❑ continuous IV	Phase III (begin 2/03)➢USA, phase III (begin 10/00, completed 2/02)➢USA (combination) ❑ advanced, Stage IIIb or Stage IV nsclc, first line
Janssen Pharmaceutica ❑ Kyowa Hakko Kogyo, Ortho Biotech Products	Tipifarnib ❑ R115777 ❑ Zarnestra	Farnesyl protein transferase inhibitor; imidazole; inhibits activated p21 ras ❑ PO	Phase III (completed 02)➢USA, Europe (combination) ❑ metastatic pancreatic cancer; phase III (completed 02) Europe ❑ metastatic colorectal cancer
Maxim Pharmaceuticals ❑ Estero Anstalt, Schering, Mayne Pharma, MegaPharm, Chiron, Viragen International	Histamine dihydrochloride ❑ Ceplene (formerly Maxamine and EpiLeukin)	H2 receptor agonist (H2ra) based on histamine dihydrochloride which specifically blocks the phagocyte signal that leads to NK-cell death, thereby allowing NK cells to retain cytotoxic function; allows certain biological response modifiers, such as cytokines to achieve their full antitumor and anti-infective potential ❑ SC	Phase III (begin 2/98, closed 9/01) ➢USA, Europe (UK), Australia, Canada, Israel, New Zealand ❑ AML; phase III (ongoing 4/02)➢Europe, Australia, Canada, Israel, phase III (begin 1/02, ongoing 6/03)➢USA, Europe, Canada ❑ metastatic (Stage IV) malignant melanoma
MGI Pharma ❑ Dainippon Pharmaceutical, U California	Irofulven [acylfulvene (6-HMAF)] ❑ MGI 114, MGI-114, NSC 683863	Semisynthetic analog of *illudin S*, a sesquiterpene isolated from the Jack o' lantern mushroom, *Omphalotus illudens* ❑ IV	Phase III (begin 2/01, closed 6/02) ➢USA ❑ pancreatic cancer
NCI	Carboxyaminoimidazole (CAI) ❑ NSC-609974	Synthetic inhibitor of 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 III (ongoing 6/03)➢USA ❑ Stage III or IV nsclc
NCI	Fenretinide (4-HPR)	Synthetic retinoid; vitamin A analog ❑ PO	Phase III (begin 11/99, ongoing 6/03) ➢USA ❑ bladder cancer (prevention); phase III (begin 6/01, ongoing 6/03) USA, Canada, Europe (Norway, UK), Australia ❑ ovarian cancer (prevention)
NeoRx ❑ Dow Chemical	Holmium-166 DOTMP (Ho166-DOTMP) ❑ Skeletal Targeted Radiotherapy (STR)	Small-molecule bone-seeking agent, complexed with the radionuclide holmium-166 (166Ho-DOTMP), a tetraphosphonate chelate radio-therapeutic with high-energy beta emission, that localizes specifically to the skeleton and delivers target-ed radiation to the bone and bone marrow; can be used as preparative regimen for radiosensitive malignancies ❑ IV	Phase III (begin 10/00, suspended 2/01, planned 6/03)➢USA ❑ multiple myeloma

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Northwest Biotherapeutics	DCVax-prostate (CaPVax)	Mature dendritic cells loaded with recombinant human prostate-specific membrane antigen (PSMA) ❑ intradermal	Phase III (begin 6/02, ongoing 6/03) ➢USA ❑ metastatic HRPC
Novartis Pharmaceuticals ❑ Schering AG	PTK-787, PTK787 (ZK-222584, ZK224584, CGP-79787)	Orally available angiogenesis inhibitor that targets KDR, c-kit and platelet-derived growth factor receptor (PDGFr) ❑ PO	Phase III (begin 2/03)➢Europe (Belgium, France, Germany, Italy, Switzerland), Brazil, New Zealand, USA (combination, CONFIRM 1), phase III (begin 1/03)➢USA (combination, CONFIRM 2) ❑ metastatic colorectal cancer
Novuspharma ❑ Bigmar	Pixantrone ❑ BBR 2778	Mitoxantrone analog; novel DNA intercalator with topoisomerase II activity and reduced cardiotoxicity ❑ IV	Phase III (begin 4/02, ongoing 6/03) ➢Europe (Italy), USA, Canada (combination) ❑ refractory indolent NHL
Onyx Pharmaceuticals ❑ PolyMASC Pharmaceuticals	CI-1042, ONYX-015, dl1520	Genetically engineered E1B-55kD gene-deleted group C adenovirus that replicates in and lyses cells lacking p53 activity ❑ intralesional, intratumoral, intraoperative, mouthwash, intra-arterial, IV, intracranial, intracerebral	Phase III (begin 6/00, suspended 1/03)➢USA, Europe (combination) ❑ recurrent or refractory head and neck cancer
OSI Pharmaceuticals ❑ Pfizer, Genentech, Roche	Erlotinib ❑ CP-358,774, OSI-774, R1415 ❑ Tarceva	Small molecule that directly inhibits EGFr tyrosine kinase; CP-373,420, a des-methyl metabolite of CP-358,774, is also a potent inhibitor of EGFr ❑ PO, IV	Phase III (begin 8/01, ongoing 7/02) ➢Australia, Canada, South Africa, New Zealand, Singapore ❑ refractory, incurable Stage IIIb or IV nsclc; phase III (begin 6/01, closed 10/02)➢USA (combination) ❑ chemotherapy-naive Stage IIIb or Stage IV nsclc; phase III (closed 4/03)➢Europe, Canada (combination) ❑ unresectable, locally advanced, or metastatic pancreatic cancer
OSI Pharmaceuticals ❑ Paladin Labs, Aventis Pharma, Roche, Eli Lilly, GlaxoSmithKline	Exisulind, sulindac sulfone ❑ FGN-1 ❑ Aptosyn (formerly Prevatac)	Sulfone metabolite of the non-steroidal anti-inflammatory (NSAI) drug sulindac; member of the class of proapoptotic drugs termed selective apoptotic antineoplastic drugs (SAAND) ❑ PO	NDA (filed 10/99, rejected 9/00) USA, phase II/III (begin 7/99, ongoing 6/03)➢USA ❑ familial adenomatous polyposis (FAP); phase III (begin 3/01, closed 3/03)➢USA (combination) ❑ previously untreated, refractory nsclc
Pfizer Global Research and Development	AG3340 ❑ Prinomastat	Synthetic selective inhibitor of certain matrix metalloprotease (MMP) enzymes such as gelatinase A and B, stromelysin-1 and collagenase-3; angiogenesis inhibitor ❑ PO	Phase III (closed 9/00)➢USA (combination), phase III (closed 12/99)➢USA (combination) ❑ advanced (Stage IIIb) nsclc, phase III (discontinued 8/00)➢USA (combination) ❑ advanced or metastatic HRPC
Pfizer Global Research and Development Ann Arbor ❑ Southern Research Institute	Acetyldinaline ❑ CI-994, GOE 5549, PD 123 654	Novel substituted benzamide, an oral histone deacetylase inhibitor, with cytotoxic and cytostatic activity ❑ PO	Phase III (closed 11/00)➢USA (combination) ❑ refractory, Stage III or Stage IV nsclc; phase III (closed 11/00)➢USA, Canada, Europe ❑ advanced pancreatic cancer
PharmActinium ❑ Organon, Protein Design Labs, MSKCC, Oak Ridge National Laboratory (ORNL), European Institute of Transuranium Elements (ITU), MedActinium, NIH	Bismuth-213-HuM195, 213Bi-HuM195, [213Bi]HuM195	Bismuth-213-labeled humanized IgG1 MAb specific for CD33; part of the Alpha Particle Immunotherapy technology platform ❑ IV, injection	Phase III (begin 11/99, completed 5/01)➢USA, Canada, UK (combination) ❑ acute myeloid leukemia (AML)

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Pharmacyclics ❑ Abbott Laboratories, U Texas, Hoechst Celanese	Motexafin gadolinium ❑ PCI-0120 ❑ Xcytrin	Gadolinium texaphyrin (Gd-Tex) that selectively accumulates in cancer cells sensitizing them to radiation ❑ IV	Phase III (completed 3/01)➢USA, Europe ❑ metastatic brain cancer; phase III (begin 12/02)➢USA, Canada, Europe, Australia ❑ lung cancer metastacized to the brain
Pharmion ❑ Pharmacia	5-Azacitidine (AzaC), 5-azacytidine ❑ NSC-102816	DNA/RNA antimetabolite ❑ SC, IV	Phase III (ongoing 1/98, completed 02)➢USA ❑ myelodysplastic syndrome (MDS)
Praecis Pharmaceuticals ❑ Sanofi-Synthelabo, Indiana U	Abarelix ❑ Plenaxis	Luteinizing hormone-releasing hormone (LHRH) antagonist ❑ IM	Phase III (completed 4/00)➢USA, NDA (refiled 2/03)➢USA ❑ advanced, refractory, hormone-dependent prostate cancer; MAA (filed 6/03)➢Europe (Germany) ❑ advanced, hormone-dependent prostate cancer
Progenics Pharmaceuticals ❑ MSKCC, Antigenics, U California, Neose Technologies	GM2-KLH/QS-21 ❑ GMK	Vaccine composed of ganglioside antigen GM2 conjugated to an immunogenic carrier protein KLH (keyhole limpet hemocyanin) and combined with the adjuvant QS-21 ❑ SC	Phase III (ongoing 8/02)➢USA, Canada, Europe, Australia, New Zealand ❑ Stage III malignant melanoma; phase III (begin 1/99, ongoing 8/02)➢Europe, Australia ❑ intermediate-risk malignant melanoma
Protein Design Labs ❑ Nippon Organon	HuM195, SMART M195 ❑ Zamyl	Unconjugated humanized murine MAb directed against the cell surface myelomonocytic differentiation antigen CD33 ❑ IV bolus	Phase III (begin 11/99, completed 5/01)➢USA, Canada, Europe (UK) ❑ refractory or relapsed AML; phase II/III (closed 12/98)➢USA ❑ AML in remission
Sanofi-Synthelabo ❑ SRI International	Tirapazamine ❑ SR 4233, SR-259075 ❑ Tirazone	Benzotriazene cytotoxic that is bioreduced under hypoxic conditions to an active free radical species which cause single and double strand DNA breaks ❑ IV, PO	Phase III (begin 7/00, completed 4/02)➢USA, Europe, Australia and Canada (combination), phase III (begin 11/00, closed 12/02)➢USA (combination) ❑ Stage IIIb or Stage IV nsclc
Schering-Plough ❑ Endorecherche	EM-800 (SCH 57050)	Third generation SERM acting as pure nonsteroidal antiestrogen; prodrug of EM-652 (SCH 57068) ❑ PO	Phase III (begin 2/98, completed 3/02)➢Canada, Europe (combination) ❑ relapsed breast cancer
Spectrum Pharmaceuticals ❑ Johnson Matthey, GPC Biotech	Satraplatin ❑ JM-216 (formerly BMS-182751)	Novel oral platinum (IV) analog ❑ PO	Phase III (begin 6/98, closed 9/99) ➢Europe, USA, phase III (closed 8/99)➢USA (combination) ❑ hormone-refractory prostate cancer
SR Pharma ❑ U College London, Sakai Chemical Industry	SRL 172	Immunotherapeutic consisting of heat-killed *Mycobacterium vaccae*; Th1 adjuvant ❑ intradermal	Phase III (begin 10/98, completed 9/01)➢Europe ❑ nsclc
StressGen Biotechnologies ❑ Whitehead Institute of Biomedical Research, Roche, NCI	HspE7, Hsp65E7 ❑ SGN-00101 ❑ CoVal fusion (Oncocine)	Adjuvant-free, recombinant fusion protein combining heat shock protein 65 (Hsp65) from *Mycobacterium bovis* Bacille Calmette-Guerin (BCG) and the E7 protein from human papillomavirus type 16 (HPV16) ❑ SC, topical	Phase III (begin 11/00, completed 8/01)➢USA ❑ high-grade anal dysplasia
SuperGen ❑ Stehlin Foundation for Cancer Research, Clayton Foundation for Research, RTP Pharma	Rubitecan ❑ RFS 2000, 9-nitrocamptothecin, 9NC, nitrocamptothecin ❑ Orathecin	Third-generation, water-insoluble camptothecin analog; topoisomerase I inhibitor, causing single-strand breaks in the DNA of rapidly dividing tumor cells ❑ PO, inhaled, IM, IV, catheter-delivered, stent-delivered	Phase III (begin 11/98, closed 2/02) ➢USA ❑ unresectable, locally advanced, or metastatic adenocarcinoma of the pancreas; phase III (closed 5/01)➢USA, phase III (closed 12/01)➢USA ❑ recurrent or refractory pancreatic cancer

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SuperGen ❑ Pharmachemie	Decitabine; dezocitidine ❑ NSC-127716, DAC ❑ Dacogen	Cytosine analog that inhibits DNA-methyltransferases, resulting in gene demethylation and reactivation ❑ infusion	Phase III (begin 3/01, ongoing 6/03)➢USA, phase III (begin 5/02, ongoing 6/03)➢Europe (The Netherlands, Germany) ❑ advanced, high-risk MDS
TAP Pharmaceutical Products	Carbamic acid ❑ TNP-470 (formerly AGM-1470)	Antiangiogenic analog of fumagillin ❑ IV, SC	Phase III (closed 7/98)➢USA ❑ locally advanced, nonresectable, nonmetastatic pancreatic cancer
Titan Pharmaceuticals ❑ U Kentucky Research Foundation, Goodwin Biotechnology	3H1 anti-Id antibody ❑ CeaVac	Murine IgG1 anti-idiotype MAb generated against the 8019 IgG1 MAb that binds the CEA epitope; mimicks CEA ❑ intracutaneous, SC	Phase III (begin 1/00, completed 02) ➢USA, Europe (UK) (combination) ❑ metastatic (Stage IV) colorectal cancer
Vical ❑ U Michigan, Boston Scientific	Allovectin-7	DNA/lipid complex containing a gene encoding for allogenic histocompatibility antigen, HLA-B7, and a lipid to facilitate uptake ❑ intratumoral	Phase III (begin 5/98, ongoing 4/02) ➢USA ❑ advanced or metastatic, malignant melanoma; phase III (completed 02)➢USA (combination) ❑ early-stage malignant melanoma
Xenova Group ❑ QLT	Tariquidar ❑ XR9576	Selective potent inhibitor of the action of the P-gp pump; may prevent chemotherapy failure attributed to drug resistance ❑ IV, PO	Phase III (begin 6/02, suspended 2/03, stopped 5/03)➢USA, Canada, Europe (combination) ❑ first line treatment of advanced (Stage IIIb), or metastatic (Stage IV) nsclc
YM Biosciences ❑ U Manitoba	Tesmilifene ❑ DPPE (formerly BMS217830)	Novel antihistamine with potent affinity for growth-regulatory intracellular receptors, enhances cytotoxic effects of chemotherapy with no additive side effects ❑ IV	Phase III (begin 8/98, closed 11/99) ➢Canada (combination) ❑ metastatic breast cancer

** Detailed descriptions of all agents included in this Exhibit are presented in NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), a subscription resource residing at www.nmok.net. Subscribers to nm|OK may view the complete record of the drugs listed in this Exhibit, by entering "malignancy" in the Therapeutic Category field and "phase III" in the Latest Development Status field, in the New Drug Module.*

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), July 2003

as to which trials, open for enrollment, are suitable for a given patient.

Individuals who participate in clinical trials typically provide consent in the belief that they are contributing to medical knowledge. But if the knowledge gained is never reported, both the trust between patients and investigators, and between patients and research ethics review boards are damaged. Ethical issues are of particular concern if industry is gaining financially from public involvement in trials, but refusing to reciprocate by making information from industry-sponsored trials generally available. All stakeholders, investigators, research organizations and institutions, journal editors, lawmakers, consumers, and others, are asked to act now, together and in their own domains, to ensure comprehensive registration of clinical trials (Dickersin K and Rennie D, JAMA, 2003;290:516-523).

Large clinical trials are the standard means for making treatment decisions, and nonpublication of the results of such trials can lead to bias in the literature, and contribute to inappropriate medical decisions. Investigators conducted a survey of 510 abstracts from large (sample size ≥200), randomized, controlled, phase III clinical trials presented at ASCO meetings between 1989 and 1998, in order to determine the rate of full publication of large randomized clinical trials (RCT) presented at annual meetings of the American Society of Clinical Oncology (ASCO), quantify bias against publishing nonsignificant results, and identify factors associated with time to publication. Trial results were classified as significant or nonsignificant, and the type of presentation and sponsorship were identified. Subsequent full publication was verified using a Medline and Embase search, completed on November 1, 2001. The search was updated in November 2002, using the Cochrane Register of Controlled Trials. Authors were contacted if the searches did not find evidence of publication.

Among the 510 randomized clinical trials (RCT), 26% had not been published in full within 5 years after presentation at the meeting; 81% of the studies with significant results had been published by this time compared with 68% of those with nonsignificant results. Studies with oral or plenary presentation were published sooner than those not presented, and studies with pharmaceutical sponsorship were published sooner than studies with cooperative group sponsorship, or studies for which sponsorship was not specified. These factors remained significant in a multivariable model. The most frequent reason cited by authors for not publishing was lack of time, funds, or other

resources. A substantial number of large phase III trials presented at an international oncology meeting remained unpublished 5 years after presentation. Bias against publishing nonsignificant results is a problem even for large RCT (Krzyzanowska K, etal, JAMA. 2003;290: 495-501).

Something also needs to be done about the lack of standardization and the poor quality of reporting of results from clinical trials. For instance, in a review of the quality of reporting of large RCT presented at ASCO meetings, the authors (Krzyzanowska MK, etal, ASCO03, Abs. 2157) found that the quality of reporting of RCT at ASCO was low. This conclusion was based on abstracts presenting results of large RCT (sample size ≥200) identified from the proceedings of ASCO meetings between 1989 and 1998. Among the 529 abstracts identified, the primary endpoint was explicitly stated in only 21%, while multiple endpoints (≥2) were reported in 74%. The number of both randomized and evaluable patients was reported in 191 abstracts, and in 36% of these the difference between the two numbers was 10% or more. A discrepancy between results and conclusions was noted in 46% of abstracts with nonsignificant results, and in 15% of those with statistically significant results. Although space precludes details required in the final report, abstracts may be improved through use of explicit minimal guidelines.

RANDOMIZED AND LARGE CLINICAL TRIALS IN ONCOLOGY

RCT are currently the standard in evaluating drugs to establish benefit over existing commercialized/standard regimens. Currently, randomized phase III, or in some cases phase II clinical trials, must be carried out in order for a developer to submit a New Drug Application (NDA) to the FDA for approval (registration) to market a drug in the USA. Similar procedures are followed in other jurisdictions. In the oncology sector, promising drugs have also been approved for commercialization on the strength of phase II clinical trial results. One case in point is imatinib (Gleevec; Novartis). In addition, developers have designed randomized phase II clinical trials whose results would be used for registration purposes. One case is point is cetuximab (Erbitux; ImClone).

Despite the lateness of RCT in the development cycle of new oncology drugs, failures occur for lack of effectiveness and/or severe adverse effects.

Ethics of Large Clinical Trials in Oncology

Dr. David F. Horrobin, now deceased from complications of mantle-cell lymphoma, published an extremely insightful paper (Lancet 2003;361:695-97) questioning the ethics of large clinical trials in rapidly lethal diseases such as late-stage cancer. In clinical trials, the larger the anticipated effect, the fewer patients need to be enrolled to show statistical significance. Conversely, the smaller the effect, the larger the enrollment needed to demonstrate effect. In most chronic conditions, such as arthritis, psoriasis, migraine headaches, etc., small effects are not sought because of the obvious prescribing problem. However, with few exceptions, most oncology drugs evaluated in clinical trials in late-stage, or rapidly progressing disease, are expected to have a small effect. Therefore, in order to justify doing the trial at all, enrollment needs to be very large.

Most large trials cannot be justified on ethical grounds. If a trial has to be large, say more than 100 patients, it is large only because the expected effect size is small. That means that most patients entering the trial have little or no chance of benefiting. Therefore, patients with advanced malignancies volunteering for large trials in cancer are being misled. Not only there is a slim chance of any benefit, but because of the toxic nature of many oncology treatment regimens, there may well be a substantial chance of harm. Although the risk of harm is usually well described in the consent form, little is said about the trial's design regarding benefit.

The effectiveness dilemma becomes obvious when drugs evaluated in clinical trials become commercially available to the patient population at large. Physicians prescribing drugs that showed statistically significant benefits in clinical trials with sizes of 20 or 30 patients, know that most treated patients will show a response that can be reasonably attributed to the drug. But as effects become smaller, and trial sizes become larger, it becomes increasingly difficult to establish the chance of a patient's response to the drug. In these cases, although the drug's efficacy appears to be shown conclusively in a large clinical trial, physicians prescribing the drug in the affected population at large have no way of assessing its value for any given patient.

Large clinical trials use power calculations to decide on enrollment size. However, these calculations rarely work in the real world. Both underpowered and overpowered large clinical trials present serious medical and ethical problems. Underpowered clinical trials yield unreliable results, while overpowered trials expose patients to treatments from which they will derive no benefit.

Why are such trials being conducted at all? While small effects do little for patients, they do benefit the drug's marketer, the recruitment community, and the participating institutions. Choosing which drugs to take to clinical trial, despite the rhetoric about saving lives, is a business decision. Currently, most large clinical trials involve new patented entities in which the drug industry has a big stake, or expansion of already commercialized drugs with still valid patents. The high cost of large trials means that they can be done only on patent-protected agents. Because drug companies are able to charge very high prices for their drugs, it is worthwhile to invest significant funds to expand the drug's use. Often, adding a new indication doubles the annual revenues of a patented drug. Even without FDA approval for additional indications, favorable results from clinical trials encourage off-label use, prevalent in oncology, significantly boosting revenues. Actually, using large clinical trials as a means to expand

drug use, although costly, is considerably less costly than seeking supplemental FDA approval. Therefore, big pharma has focused its drug development efforts in obtaining the most benefit from its existing product line rather than taking the risk of shepherding novel agents through all the pitfalls of drug development. Without patent protection, it is unlikely that a developer would undertake clinical trials of the many compounds that might have a therapeutic effect. The sheer prohibitive cost associated with clinical drug development has drastically reduced the range of compounds from which new treatments can be drawn. It is unlikely that a compound not protected by patent would be developed, even if there is good science behind claims of effectiveness.

Approval to conduct some of these large trials, provided by the participating institutions, questions their motives. It is true that the clinical trial sector has also become big business. Most large oncology franchises have become adept at performing these trials, and many institutions conducting large trials have found that despite their complexity and cost, they can be a great source of income. In reviewing the protocol of some combination trials of commercially available chemotherapeutics, it is incredible that the investigators succeeded in recruiting enough patients to conduct a sufficiently powered study whose result would justify its cost. In many of these cases, smaller trials of similar combinations, reported in the literature, produced no benefit.

The way large trials are justified is by the fact that occasionally patients do very well. Investigators often gush over a trial describing a drug that adds 5 months of life to a few patients gained as a result of grueling treatment regimens. However, even in this case, the evidence base is near useless as a guide to what is likely to happen in an individual patient's case, partly because the exclusion and inclusion criteria for trials are often so narrowly drawn, that most individuals are unlikely to fit them. For instance, in order to produce favorable results, trials limit participation to patients in late-stage disease fitting narrow entry criteria based on disease characteristics. It is impossible to adhere to such strict guidelines when drugs are used in clinical practice. In view of the frequent severe adverse events, usually much more predictable and reliable in their occurrence than is a therapeutic response, patients' decisions not to be treated should not be considered irrational.

Interestingly, when the widely held belief that cancer patients enrolled in clinical trials have better outcomes compared to patients treated outside of the research setting was tested, it was revealed that median survival time (MST) of patients treated outside the clinical trial setting is comparable to that of patients treated in pivotal RCT. To test this hypothesis as it pertains to metastatic colorectal cancer treated through the provincial Cancer Care Ontario's New Drug Funding Program (NDFP), the provincial drug utilization database was linked with the death registry. Records of the 1,741 patients treated with first line (n=1010), and second line (n=731) with irinotecan-based chemotherapy, between January 1998 and December 2001, were linked with death statistics. Survival was measured from date of first irinotecan administration until September 2002. MST of patients treated with first line irinotecan was 17 months with a median duration of therapy of 4.0 months, which compared favorably to the large RCT that reported MST of 14.8 months to 17.4 months (Evans WK, etal, ASCO03, Abs. 1505).

Dr. Horrobin correctly concludes, that despite huge expenditures, success in developing effective anticancer treatments has been elusive. The few outstanding successes in rare cancers cannot hide the overall failure. This situation has to mean that there is a real possibility that standard approaches used in investigating treatment options are wrong, and need to be changed. Dr. Horrobin suggests that one approach that might result in a more sane drug development process in oncology, is to abandon most large-scale clinical trials looking for small effects, and instead do large numbers of small trials, often in single centers, looking for large effects.

There is no doubt that for the benefit of science and patients, the best approach is to fund small trials with novel agents that may actually produce big effects. However, because financial decisions in the oncology sector are made based on business criteria, the only way to stem the tide is to persuade investigators, patient advocates, and consumers alike to be far more selective about the trials they become involved with.

The need for large clinical trials looking for small effects may be obviated by new scientific developments. Prevailing clinical trial designs will change dramatically because of the understanding of the mechanisms involved in many aspects of cancer, from carcinogenesis, to the maintenance of the malignant state, to metastasis. In this new environment, clinical trials would need to be designed to test a drug or regimen on patients whose tumors exhibit specific well defined characteristics, thus eliminating the current problem of large clinical trials involving patients with heterogeneous disease.

The Impact of Pharmacogenomics

Pharmacogenomics, as the name implies, is the science that explains how an individual's genetic makeup affects response to drugs. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with genetics, proteomics, and single nucleotide polymorphisms (SNP), to profile an individual's likely response to a certain drug. Although age, and environmental and lifestyle issues may influence one's response to medicines, it is believed that the genetic makeup will be the critical factor in creating personalized drugs with greater efficacy and safety.

In oncology, advances in pharmacogenomics may one day allow for the development of drugs that are tailor-made

to groups of patients whose tumors share certain intrinsic markers and/or other genetic factors that predisposes them to a certain response to an anticancer agent. Eventually, pharmacogenomics may provide information on the probability of metastasis, and the likelihood of cancer recurrence, and predict outcome for individual patients. Off course, treatment-predictive pharmacogenomics will not be put into clinical practice until this approach is validated.

Design of Clinical Trials for New Molecularly Targeted Compounds

Many new agents addressing specific molecular targets have entered clinical development or are being considered for development. The requirement of a measure of target effect (tissue or imaging) is now commonly included in early trials of new targeted compounds, in an attempt to demonstrate proof-of-principle as well as guide dose selection. Phase II clinical trial designs including novel correlative, imaging and clinical endpoints, are currently being tested. Alternate endpoints such as progression or time-to-progression (TTP), are being increasingly considered, and novel approaches such as randomized discontinuation designs (RDD), multinomial designs, and growth modulation indices are being prospectively tested (Seymour L, Curr Pharm Des 2002;8(25):2279-84).

Randomized Discontinuation Design

Randomized discontinuation design (RDD) takes into effect one of the problems encountered in large RCT, namely heterogeneity of tumor growth rates in the population of patients enrolled in the trial. An appropriate trial design is necessary to distinguish antiproliferative activity attributable to the novel agent from indolent disease.

RDD has been proposed that can segregate those patients with tumors growing at comparable rates. In an RDD approach, all patients enrolled in a trial are treated with the study agent (stage 1). Subsequently, only those patients whose disease is stable are randomized in a double blind fashion to continuing therapy or placebo (stage 2). This design allows the investigators to determine if an apparent slow tumor growth is attributable to the drug, or to selection of patients with naturally slow growing tumors. By selecting a more homogeneous population, the randomized portion of the trial requires fewer patients than would a study randomizing all patients at entry. The design also avoids potential confounding because of heterogeneous tumor growth. Because the two randomly assigned treatment groups each comprise patients with apparently slow growing tumors, any difference between the groups in disease progression after randomization is more likely a result of the study drug and less likely a result of imbalance with respect to tumor growth rates. Stopping rules during the initial open-label stage, and the subsequent RCT, allow reduction of the overall sample size.

Also, expected average tumor growth rate is an important consideration when deciding the duration of follow-up for the two RDD stages. RDD is a feasible alternative phase II study design for determining possible activity of cytostatic anticancer agents (Rosner GL, etal, J Clin Oncol, 15 Nov 2002;20(22):4478-84).

Relationship Between Response Rate and Survival

In the past decade response rates have become the Holy Grail in the search for better anticancer treatment regimens. Patients with incurable cancer are faced with difficult decisions about whether or not to be treated by chemotherapy in an attempt to preserve the quality and/or prolong the quantity of their lives. While clinical trials often provide oncologists with information about tumor response rates and treatment toxicity, the average prolongation of survival with treatment, compared to best supportive care, has not been well described.

In order to explore whether there is a relationship between tumor response rate and prolongation of MST in patients with incurable malignancies, a literature search was performed using PubMed combined with an expert survey, to identify trials comparing cytotoxic chemotherapy to best supportive care for a variety of malignancies. Among 25 controlled RCT comparing cytotoxic chemotherapy to best supportive care for a variety of malignant conditions identified in this search, 16/25 were in patients with nsclc. Data was extracted and analyzed regarding response rates, stable disease rates, 1-year survival, 2-year survival, and MST, in those randomized to chemotherapy, compared to those randomized to supportive care with or without a placebo. Sample sizes in these trials ranged from 36 to 300 patients, with a mean sample size of 138 patients.

Response rates in the treatment arms ranged from 0% to 50%. There was a relationship between response rate and survival. Each 2% response rate above 15% correlated, on average, with a 1 week increase in survival. In 80% of trials reporting a response rate of at least 20%, there was a >10% increase in 1-year survival, compared with best supportive care. On average, 1-year survival increased 20% in trials of agents with at least a 20% response rate. This suggests that, on average, 1 additional patient will be alive at one year for every 5 patients treated with chemotherapy regimens with a response rate of at least 20%. The mean increase in 1-year survival for trials of agents with <20% response rate was 3% (Shanafelt TD, etal, ASCO03, Abs 2983).

OVERSIGHT IN CLINICAL DEVELOPMENT OF ANTICANCER DRUGS

Currently, the oncology drug development sector is progressing in a feverish, chaotic pace. Therefore, oversight has become particularly important in ensuring that investigation of potentially life-saving therapies proceeds on a timely, ethical and scientifically sound fashion. Ultimately, oversight is expected to impact many aspects of clinical development of anticancer agents.

Centralized Review Boards

Currently, approval for the initiation of clinical trials rests with individual institutional review boards (IRB). In May 2000, ASCO formed a taskforce to reform the review process after investigations of deaths among patients participating in clinical trials at some of the USA's most prestigious research institutions found major violations of protocols, serious under-reporting of adverse events, and inadequate federal and institutional oversight. The taskforce found that the increasing numbers of trials they need to review and the complexity of their design overwhelm many local IRB. In addition, because so many trials today are multicenter, scores of different local IRB, each with slightly different policies and protocols, may be overseeing one trial. In some cases more than 100 different IRB might be involved in a trial's approval and oversight.

To address this issue, ASCO proposed a "stepwise" introduction of centralized review in which protocols would first go to a few regional central review board (CRB), which would provide scientific and ethical review. This change is intended to standardize and streamline the review process, improve patient safety, and help restore the public's confidence in clinical research.

To test this approach, the NCI is sponsoring a pilot program that centralizes the review process in multicenter, randomized phase III clinical trials. This review process mirrors the centralized reviews of all NCI-sponsored trials being conducted by the NCI cancer cooperative trials group, before being submitted to local IRB review. In the pilot program participating centers may refer all their IRB functions to the CRB, or retain some role in overseeing implementation of the protocol and reporting adverse events to the CRB. This new review system is expected to ensure consistency in quality of review, avoid duplication, and make the process more efficient.

Beginning with only 22 participating centers, this pilot program now provides centralized review to 130 centers. The CRB membership draws from a variety of participants, including IRB chairs and members, clinical investigators, scientists, drug company representatives, and consumer advocates. As it is structured currently, 25% of members are consumer advocates.

Conflict of Interest Guidelines

ASCO also announced tough new conflict of interest guidelines that expand disclosure requirements for researchers submitting abstracts and papers to ASCO meetings and its publications. These guidelines severely limit the financial interest leaders of trials can have in companies and products involved in such trials. The new conflict-of-interest policy requires that researchers submitting abstracts or making presentations at ASCO's annual meeting, authors submitting papers to the JCO, and anyone sitting on ASCO's board or committees, must disclose almost all financial ties. Such disclosures include a commercial interest in the treatment under investigation, money earned for advisory work, stock ownership, research funding and remuneration for trips unrelated to research, and travel and gifts with a value over $100.

In addition, professionals holding leadership roles in trials, including principal investigators, members of the trial's executive committee, members of the data safety monitoring board, will be prohibited from having any substantial financial conflicts-of-interest involving all aspects of the trial. Such conflicts include ownership of stock in the trial's sponsor, royalties, licensing fees, or patents related to the product or treatment under investigation, and positions as an officer, board of directors' member, or employee of the trial's sponsor. Researchers are also prohibited from accepting payment for referring patients to a trial, accepting payment for particular research outcomes, or for signing contracts that allow the sponsor to override the decision to publish, or present trial results (McCarthy M, Lancet, 10 May 2003;361:9369).

DRUG COMBINATION STRATEGIES IN ONCOLOGY

Combination treatments are becoming the mainstay for the management of advanced or metastatic cancer. Better understanding of the mechanism of the various drugs incorporated in combination regimens have yielded a somewhat better survival at tolerated toxicity, improving QoL. Promising data from numerous clinical trials pairing various established cytotoxics acting on different mechanisms, or combining cytotoxics with novel regulatory or immunotherapy drugs, is encouraging the adoption of such treatment approaches in new trials and in the clinic.

Currently, hundreds of trials are ongoing combining established cytotoxic drugs, and other modalities, for treatment of almost all types of tumors. One of the new challenges in combination/multimodality regimens is assessing the role of cytostatic agents when combined with standard cytotoxic chemotherapy. Novel agents are also being combined with numerous commercially available cytotoxics, i.e. taxanes (see FO, pp 1422-1528), and cytotoxic antibiotics (see FO, pp1529-1592), among others. Lately, clinical trials are also being designed combining novel regulatory and/or immunotherapy agents without a cytotoxic component.

Combination therapies are poised to create new options for patients with advanced/metastatic colorectal cancer, nsclc, mesothelioma and prostate cancer, among others. Results from pivotal trials of promising combination regimens, as well as monotherapies, reported during ASCO03, are described later in this issue.

Colorectal Cancer

From being a thoroughly neglected drug treatment target for decades, advanced or metastatic colorectal cancer is evolving into a highly contested global market, already serviced by newly introduced agents, and poised to support several novel drugs currently seeking FDA approval. Irinotecan, the current gold standard in combination therapies in first line or second line treatment of advanced/

metastatic colorectal cancer, is joined by oxaliplatin as a treatment option with or without irinotecan, for the same indications.

One regimen showing activity in colorectal cancer in the adjuvant setting, consists of oxaliplatin plus 5-fluorouracil/leucovorin (5-FU/LV). Results from the MOSAIC trial demonstrated that the addition of oxaliplatin to the current post surgery standard chemotherapy of 5-FU/LV, reduces risk of recurrence by 23%. This gain was obtained with a favorable safety profile.

Oxaliplatin also improved survival in metastatic colorectal cancer. In a phase II clinical trial (protocol ID: N 9741), sponsored by the North Central Cancer Treatment Group (NCCTG), a regimen of oxaliplatin plus 5-FU/LV (FOLFOX4) as first line treatment for metastatic colorectal cancer, resulted in an overall survival of 19.5 months, compared with 14.8 months for the standard irinotecan plus 5-FU/LV (IFL) regimen, representing a survival gain of more than 30%. The FOLFOX4 regimen was superior in terms of response rate, progression-free survival (PFS), overall survival and safety (Pitot HC, etal, ASCO03, Abs. 1048).

Based on these results, Sanofi-Synthelabo (Paris, France) is expected to file an sNDA with the FDA for approval of oxaliplatin in the USA for first line treatment of metastatic colorectal cancer in the second half of 2003, and for the adjuvant treatment of colorectal cancer, towards the end of 2003. The filing in Europe in the adjuvant setting should occur in the second half of 2003.

Results from other late stage clinical trials of novel agents in advanced/metastatic colorectal cancer are described later in this issue.

Lung Cancer

Lung cancer is becoming the chief battlefront in the fight against cancer, mostly because of its high global incidence, the need for effective therapies, and the commercial opportunity. Little has advanced in the treatment of nsclc since the advent of the taxanes and gemcitabine in the mid-1990s. Currently, improvements in the treatment of nsclc are only potentially achievable through the development of novel agents. A number of novel agents are beginning to emerge, with gefitinib (Iressa; AstraZeneca) being the first to obtain approval in the USA, in May 2003, as monotherapy for nsclc in the third line treatment setting. Other novel agents showing activity in this area, include erlotinib (Tarceva; OSI Pharmaceuticals), cetuximab (Erbitux; ImClone Systems), and LY900003 (Affinitak; Isis Pharmaceuticals), among others.

Mesothelioma

New treatment options, such as premetrexed (Alimta; Lilly) and bevacizumab (Avastin; Genentech) may offer some promise in the treatment of malignant pleural mesothelioma (MPM), a recalcitrant malignancy associated with high mortality and poor QoL. In the USA, Eli Lilly is in the process of filing a rolling NDA for use of Alimta, in combination with cisplatin, in the treatment of MPM, based on the largest RCT conducted in MPM, which included such endpoints as survival, tumor response, and QoL.

Prostate Cancer

An interesting development in the prostate cancer area involves immunotherapies for HRPC. Two such approaches, Dendreon's (Seattle, WA) Provenge vaccine, and Therion Biologics' (Cambridge, MA) multipart PSA-based vaccine, may prove effective in treating prostate cancer patients with advanced disease.

Biochemotherapy in Metastatic Melanoma

One prominent unexpected failure involves a biochemotherapy regimen in advanced/metastatic melanoma. A multinational, randomized, phase III clinical trial (protocol ID: EORTC 18951), conducted by the EORTC Melanoma Group in Europe, to evaluate the combination of dacarbazine (DTIC), cisplatin and IFN-α2b, with or without IL-2 (Proleukin; Chiron) in advanced melanoma, was designed to detect an improvement in 2-year survival rate from 10% to 20%. Between 1995 and 2000, 363 patients were randomized in 25 centers to treatment with DTIC (250 mg/m^2), on days 1-3, cisplatin (30 mg/m^2) on days 1-3, and IFN-α2b (10 MU/m^2) on days 1-5, and were randomized to no IL-2 (arm A) versus an IV decrescendo IL-2 schedule on days 4-9 (arm B). At final analysis, a total of 328 deaths were reported within a median follow-up of 3.4 years. MST was 9.0 months in each arm, and the 2-year survival rate was 12.9% and 17.6% in arms A and B, respectively, a difference that was not statistically significant. The estimated hazard ratio (arm B versus arm A) was 0.90.

There was also no significant difference for both secondary endpoints such as PFS (3.0 months in arm A versus 3.9 months in arm B), and response rate (22.8% versus 20.8%). Arm B was associated with a higher incidence of Grade 3/4 hypotension, fever, lethargy, anorexia, and diarrhea during the treatment period. Despite its activity in advanced melanoma as a single agent, or in conjunction with IFNα, IL-2 has no clinically relevant activity in this setting (Keilholz U, etal, ASCO03, Abs. 2848).

MARKETS OF NEW ANTICANCER DRUGS

The global market opportunity associated with the treatment of cancer has intensified big pharma's efforts to participate in this sector. After some years of neglect, the successful introduction of several novel anticancer agents in the 1990s, and the last four years, has served to refocus and expand internal and partnered projects in oncology. Anticancer agents introduced since 1990, whose markets are still growing, some of them robustly, represent a $10 billion global market (Exhibit 2). In addition, the cancer sector supports adjunct therapies from growth factors to antiemetics to analgesics, among others, that are generating

billions of dollars of revenue on their own.

Despite the fact that most anticancer drugs may not reach blockbuster status, a portfolio of cancer drugs that allows the manufacturer/marketer a high degree of market synergism, may result in a lucrative business. One successful strategy is reflected by AstraZeneca's oncology drug operations to date. In the second half of 2003, the company's oncology franchise posted worldwide revenues of $1,271 million. Among the drugs in AstraZeneca's portfolio, combined sales of three agents surpassed $1,000 million.

Another successful portfolio is represented by the Roche/Genentech alliance. Rituxan has become a blockbuster drug, Herceptin has passed the $0.5 billion mark and Xeloda the $0.25 billion mark. Markets of all these drugs have grown at over 30% in the first half of 2003.

A successful launch of a novel targeted anticancer agent involves Gleevec/Glivec. In 2002, worldwide sales of Gleevec/Glivec were $617 million, $213 million in the USA and $402 million outside the USA, only a year and one-half after its introduction in the USA in May 2001. Sales continue to grow to reach $515 million, $145 million in the USA, up 43%, and $370 million outside the USA, up 110%, in the first half of 2003, up 102% from the comparable 2002 period.

Exhibit 2
Worldwide Markets of Selected Novel Anticancer Agents[1] with Revenues of >$100 Million Introduced Since 1990

Agent Brand Name	Supplier	2002 Sales ($ millions)[2]
Arimidex	AstraZeneca	331.0
Casodex	AstraZeneca	644.0
Iressa	AstraZeneca	>100 (FY 2003)
Taxotere	Aventis	1,261.0
Campto	Aventis	241.0
Taxol	Bristol-Myers Squibb	857.0
Thalidomide	Celgene	119.0
Proleukin	Chiron	114.0
Gemzar	Eli Lilly	874.6
Herceptin	Genentech	645.0
Topotecan	GlaxoSmithKline	141.0
Doxil (USA); Caelyx (ROW)	Johnson & Johnson/ Schering-Plough	>100.0
Gleevec (USA), Glivec (ROW)	Novartis	617.0
Femara	Novartis	175.0
Camptosar	Pharmacia/Pfizer	574.0
Ellence	Pharmacia/Pfizer	333.0
Xeloda	Roche	284.0
Furtulon	Roche	159.0
Rituxan (USA), MabThera (Europe)	Roche/Idec Pharmaceuticals/ Genentech	1,494.0
Eloxatin	Sanofi-Synthelabo	389.0
Fludara	Schering AG/ Berlex Laboratories	149.0
Temodar/Temodal	Schering-Plough	278.0

[1]Excludes adjunct therapies [2] €:$ 1:1
Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), August 2003.

In a cooperative spirit, since 1996, using the accelerated (or sub part H) approval process, the FDA has approved 19 NDA/sNDA involving 17 distinct anticancer agents (Exhibit 3). This process, described in the NDA regulations, was originally championed by AIDS activists, and was adopted to allow speedy approval of antiviral drugs. Accelerated approval is granted to drugs that treat life-threatening conditions. In order to qualify, a drug must either be the only available treatment, or provide a meaningful therapeutic benefit over available treatments.

To date, most of the accelerated approvals have been based on objective tumor responses in single-arm, phase II clinical trials, in refractory malignancies, and not on RCT, which is the prevailing method for drug approval. Accelerated approval requires that the drug's developer show clinical benefit by conducting additional clinical trials.

However, once the drug enters the market, it may be difficult to initiate and complete RCT to demonstrate such important endpoints as effectiveness and safety. To date, clinical benefit has been established for only three of the 19 approved indications, and such benefit has yet to be shown for all indications granted accelerated approval since 1999.

Another means available to FDA regulators to speed drug approval is granting agents 'fast track' designation. Part of the FDA Modernization Act (FDAMA) of 1997, the fast track program is designed to facilitate development and expedite review of new drugs that treat a serious or life-threatening condition for which no appropriate treat-

Exhibit 3
Anticancer Agents Granted Accelerated Approval by the FDA (1996-2003)

Year	Drug and Indication
1996	In May 1996, the FDA granted accelerated approval for Taxotere for treatment of locally advanced or metastatic breast cancer which progressed during anthracycline-based therapy, or relapsed during anthracycline-based adjuvant therapy*.
1996	In June 1996 Camptosar was granted accelerated approval by the FDA for second-line treatment of metastatic colorectal cancer, which has recurred or progressed following 5-FU-based therapy*.
1998	In April 1998 Xeloda was granted accelerated approval by the FDA as third-line treatment of metastatic breast cancer, refractory to both paclitaxel and an anthracycline-based regimen*.
1999	In February 1999, the FDA granted Ontak accelerated approval in previously-treated, persistent or recurrent CTCL expressing the CD25 component of IL-2r.
1999	In April, 1999, the FDA granted accelerated approval to DepoCyt for the treatment of lymphomatous meningitis.
1999	In June 1999, the sNDA for Doxil was granted accelerated approval for the treatment of metastatic ovarian cancer refractory to both paclitaxel- and platinum-based chemotherapy regimens.
1999	In August 1999, the FDA granted accelerated approval to oral Temodar for the treatment of adult refractory anaplastic astrocytoma, at first relapse, that progressed on a nitrosourea- and procarbazine-containing drug regimen.
1999	In December 1999, the FDA granted accelerated approval to Celebrex as an adjunctive treatment for patients with familial adenomatous polyposis (FAP).
2000	In May 2000, the FDA granted accelerated approval to Mylotarg for treatment of patients aged 60 or older, with CD33-positive, relapsed, acute myeloid leukemia (AML).
2001	In May 2001, the FDA granted accelerated approval to Gleevec for advanced, in blast crisis accelerated phase or in chronic phase, chronic myelogenous leukemia (CML), after failure of IFN-α therapy.
2001	In May 2001, Campath was granted accelerated approval by the FDA for refractory chronic lymphocytic leukemia (CLL).
2002	In February 2002, the FDA granted accelerated approval to Gleevec for the treatment of Kit (CD117)-positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors (GIST).
2002	In February 2002, Zevalin received two separate approvals, a full approval in relapsed follicular lymphoma that no longer adequately responded to Rituxan, and an accelerated approval, in relapsed or refractory, low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL.
2002	In August 2002, Eloxatin was granted accelerated approval by the FDA, in combination with infusional 5-FU/LV, for an unmet medical need in advanced colorectal cancer that recurred or progressed following bolus 5-FU/LV plus irinotecan therapy.
2002	In September 2002, the FDA awarded accelerated approval for an sNDA for Arimidex (anastrozole) for the adjuvant treatment of hormone-receptor positive early breast cancer in postmenopausal women.
2002	In December 2002, the FDA granted accelerated approval to Gleevec for first line treatment of adult, newly diagnosed, Philadelphia chromosome-positive (Ph+) CML.
2003	In May 2003, Velcade was granted accelerated approval by the FDA as third line treatment for relapsed or refractory multiple myeloma.
2003	In May 2003, Iressa was granted accelerated approval by the FDA for third line treatment of advanced non-small-cell lung cancer (nsclc).
2003	In June 2003, the FDA granted accelerated approval to Bexxar for the treatment of CD20-positive, follicular, NHL, with and without transformation, refractory to rituximab, and having relapsed following chemotherapy.

**Clinical benefit was subsequently established*

ment exists. Fast track designation allows the drug's developer scheduled meetings to seek FDA input into development plans, the option to submit an NDA in sections (rolling NDA) rather than all components at once, and to request evaluation of trials using surrogate endpoints. Fast track is independent of priority review and accelerated approval. More than 36 novel anticancer agents in development have been granted fast track designation.

Priority review is assigned to an application for approval after it has been submitted to the FDA. Under FDAMA, NDA reviews are designated as either standard or priority. A standard designation requires that the FDA act on the application within 10 months after the date it was filed, while a priority designation sets the target date at 6 months. A priority designation is intended for those products that address unmet medical needs. Since 1995, over 45 NDA or sNDA applications, involving 31 anticancer agents, were assigned priority review.

NOVEL AGENTS IN RANDOMIZED CLINICAL TRIALS REPORTED AT ASCO03

The agents described below have been selected because results from RCT were reported during ASCO03.

Æ-941

Æ-941 (Neovastat), under development by Aeterna Laboratories (Quebec City, Canada), is a shark cartilage extract with antiangiogenic properties, primarily inhibition of vascular endothelial growth factor (VEGF) signaling, matrix metalloproteinase (MMP) activity, and induction of endothelial cell apoptosis. Æ-941 is in phase III clinical trials in nsclc and renal cell carcinoma (RCC). In October 2002, the FDA granted Æ-941 orphan drug status for the treatment of RCC.

As of July 2003, a phase III clinical trial (protocol IDs: MDA-ID-99303; NCI-T99-0046; NCCAM; RTOG 02-70) of Æ-941, in combination with induction chemotherapy and concomitant chemoradiotherapy for Stage III nsclc, initiated in March 2000, was ongoing at over 40 centers in North America. In October 2002, the Radiation Therapy Oncology Group (RTOG) joined the Community Clinical Oncology Program (CCOP) in carrying out the phase III clinical trial with Æ-941 in nsclc. This trial, sponsored by the NIH and led by the University of Texas M. D. Anderson Cancer Center (MDACC; Houston, TX), should be completed in 2005. William K. Evans, MD, of the University of Ottawa in Canada, and Charles Lu, MD, of MDACC, are the PI of this trial. Over 750 chemotherapy-naive patients will be recruited for this trial whose endpoints include determination of MST, progression-free survival PFS, tumor response, tumor-response duration, and disease-free survival (DFS).

Patients are administered AE-941 (240 ml/day) in combination with cisplatin and vinorelbine, or carboplatin and paclitaxel, depending on site of enrollment. In one regimen, carboplatin (AUC=6) and paclitaxel (200 mg/m^2) are administered for 2 cycles, followed by chemoradiotherapy consisting of radiation therapy (60 Gy/30 fractions) and weekly carboplatin (AUC=2) and paclitaxel (45 mg/m^2) for 6 doses. In the other regimen, cisplatin (75 mg/m^2) is administered on day 1, and vinorelbine (30 mg/m^2) on days 1 and 8, for 2 cycles, followed by chemoradiotherapy with cisplatin (75 mg/m^2), on day 1, and vinorelbine (15 mg/m^2), on days 1 and 8, for 2 cycles. IV cisplatin is administered on days 1, 22, 50, and 71 and IV vinorelbine on days 1, 8, 22, 29, 50, 57, 71, and 78, or IV carboplatin over 30 minutes and IV paclitaxel IV over 3 hours on days 1, 22, 50, 57, 64, 71, 78, and 85. Oral Æ-941 or placebo (120 ml), twice daily, is started in both regimens with induction chemotherapy, and continued after chemoradiotherapy as maintenance therapy. Treatment continues in the absence of unacceptable toxicity. Patients are followed every 8 weeks for 24 months.

A data safety board review of the first 40 patients who completed chemoradiotherapy was performed in April 2002. Excess or differential toxicity between the Æ-941 and placebo arms was not observed. Between June 2000 and November 2002, 200 subjects had been randomized. Blinded, overall toxicity data, available on 94 and 91 subjects during induction chemotherapy and chemoradiotherapy, respectively, form the basis of this report. Among 94 patients (Stage IIIb=59%) treated with induction chemotherapy, 18% experienced Grade 3 or 4 granulocytopenia, 2% leukopenia, and 5% neutropenic fever. Among 91 patients treated with chemoradiotherapy, 1% experienced Grade 3 or 4 granulocytopenia, 4% leukopenia, 4% thrombocytopenia, and 2% neutropenic fever. There were no deaths. A myocardial infarction, suffered by a patient during chemoradiotherapy, was the only Grade 4 nonhematologic toxicity observed. During induction chemotherapy, Grade 3 anorexia, nausea, vomiting, arthralgias, myalgias occurred in <4% of patients. The most common Grade 3 nonhematologic toxicity during chemoradiotherapy was esophagitis (19%) and dyspnea/pneumonitis (5%). To date, the overall toxicity of this aggressive chemoradiotherapy regimen appears acceptable. Accrual to this NCI-sponsored intergroup trial continues (Lu C, etal, ASCO03, Abs. 2665).

Another target of AE-941 is metastatic RCC. Enrollment in a multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial of AE-941 that began in May 2000 in Argentina, Europe and North America, for the treatment of metastatic RCC refractory to immunotherapy, was closed in December 2001. A total of 302 patients who failed to respond to standard chemotherapy were recruited at 50 centers. The primary endpoint was MST and statistical hypothesis was improvement from 8 to 12+ months. TTP, 1-year survival rate, QoL, ORR, and duration of response were secondary endpoints. Patients were administered AE-941 (120 ml) twice daily, or placebo. The lead investigators are Gerald Batist, MD, at McGill University (Montreal, Canada), Ronald Bukowski, MD, at the Cleveland Clinic Cancer Center, and Bernard Escudier, MD, at the Institut Gustave Roussy (Villejuif, France).

This trial was based on results from a phase II clinical trial in RCC that showed a statistically longer MST of 16.3 months versus 7.1 months in patients treated with AE-941 at 240 ml/day versus 60 ml/day, respectively. Eligibility criteria consisted of unresectable metastatic RCC, measurable disease, progressive disease after immunotherapy, and adequate bone marrow, hepatic and renal functions. Patients were stratified according to performance status (0 versus 1) and number of metastatic sites (1 versus >1), and were randomized 1:1 in a double-blind fashion to AE-941 (120 ml) twice daily, or placebo. From May 2000 to January 2002, 302 patients were recruited in 46 centers; performance status of 52% of patients was ECOG 0, metastases were restricted to one site in 75 patients, and in more than one metastatic site (lung=70%, liver=25%, bone=29%) in 227 patients. The safety profile of AE-941 appears acceptable with no severe toxicity seen in either arm according

to an independent Data Safety Monitoring Board (DSMB) review (Escudier B, etal, ASCO03, Abs. 844).

This trial is still at the patient survival monitoring stage, which is its primary endpoint. Following discussions with the FDA, the Canadian Health Products and Food Branch and the UK Medicines Control Agency, trial analysis will start when the number of deceased patients has reached 230. Furthermore, it has been agreed with these health authorities that should that number not be reached by September 30, 2003, trial analysis would begin at that time, and all patients still taking part in the trial would be treated with AE-941. As of June 2003, the number of deceased patients stood at 218.

Atrasentan

Atrasentan (ABT-627), under development by Abbott Laboratories, is an orally bioavailable endothelin A (ETA) receptor (ETAr) antagonist. ETAr binds with high affinity to endothelin-1 (ET-1), which stimulates proliferation in human cancer cells and is a potential mediator of prostate cancer progression. ET-1 concentrations are elevated in metastatic prostate cancer. The FDA has designated atrasentan as a 'fast-track' review candidate in prostate cancer. ET-1 is also overexpressed in other malignancies such as breast, ovarian, and colon cancer. Atrasentan is under development for the treatment of various solid tumors, including prostate, colon, breast, kidney, lung, pancreatic, cervical, ovarian, and brain cancer.

Atrasentan (10 mg) is being evaluated in randomized phase III clinical trials in prostate cancer, one in metastatic and the other in advanced HRPC. The rational and protocol for these trials are based on results of two randomized, double-blinded, phase II clinical trials involving 419 men with metastatic HRPC that suggested a response to 10 mg of atrasentan in a variety of clinical measures, including TTP.

In the phase II clinical trials, the most common adverse events with a once daily regimen included peripheral edema (38%), rhinitis (28%), headache (23%), constipation (22%), anemia (19%), and nausea (21%). Incidence of peripheral edema, rhinitis, and headache seemed to be dose-related. Asthenia (25%) and bone pain (31%) were common in both the placebo and atrasentan groups and were attributed to the disease. In order to assess the long-term tolerability of atrasentan in men with prostate cancer, a total of 220 patients from the randomized phase II clinical trials were enrolled in an open-label extension trial of 20 mg or 30 mg of atrasentan, at Sidney Kimmel Comprehensive Cancer Center, (Baltimore, MD). The most commonly reported adverse events for subjects previously exposed to atrasentan versus placebo, were similar, including peripheral edema (40% versus 44%), bone pain (31% versus 35%), anemia (25% versus 27%), asthenia (24% versus 21%), and rhinitis (23% versus 19%). No significant hepatic or renal toxicity was associated with prolonged exposure to atrasentan at higher doses. Patients with baseline renal insufficiency or liver function abnormalities did not experience any clinically significant toxicity with prolonged exposure. Long-term tolerability of prolonged administration of atrasentan at higher doses of 20 mg or 30 mg were similar to that of 10 mg in the phase II double-blinded trials. These data suggest a margin of safety for the once daily 10 mg dose currently under study in phase III clinical trials (Eliopoulos HB, etal, ASCO03, Abs. 1723).

The biologic activity of atrasentan was also evaluated in the open-label extension trial in 78 patients who had been previously treated with placebo in the double-blinded trials. A comparison of baseline laboratory values validated these patients' advanced state of disease at the start of atrasentan treatment. In an assessment of the effect of atrasentan on 5 key laboratory markers of disease, atrasentan attenuated rises in total and bone alkaline phosphatase, acid phosphatase, and lactate dehydrogenase (LDH) in this population with very advanced disease. Although the PSA slope remained constant, the effect on other bone markers and tumor burden variables suggests that atrasentan may have biologic activity in patients with very advanced prostate cancer (Carducci MA, etal, ASCO03, Abs. 1587).

To assess the potential use of atrasentan in solid tumors other than prostate cancer, its adverse event profile was compared in 5 phase I clinical trials, at atrasentan doses ranging from 2.5 mg/day to 95 mg/day, on subjects with either metastatic prostate cancer (n=44) or other solid tumors (n=61), including colon, lung, renal cell, and cervical cancer. There were no statistically significant difference in adverse events between these groups, other than those affecting the urogenital system, such as hematuria and urinary incontinence, which occurred more frequently in subjects with prostate cancer, and were considered disease related.

	Prostate Cancer (n=44)		Other Solid Tumors (n=61)	
Adverse Events	<10 mg (n=11)	≥20 mg (n=33)	<10 mg (n=7)	≥20 mg (n=54)
Headache	5 (45%)	22 (67%)	3 (43%)	42 (78%)
Peripheral Edema	8 (73%)	21 (64%)	5 (71%)	26 (48%)
Rhinitis	7 (64%)	29 (88%)	2 (29%)	41 (76%)

Headache, rhinitis, and peripheral edema occurred in both groups, and reflect the vasodilatory properties of atrasentan. Headache and rhinitis occurred to a greater extent in patients treated at a dose of ≥20 mg, suggesting dose relation. In general, adverse events were mild to moderate in severity with few resulting in treatment discontinuation (Zonnenberg BA, etal, ASCO03, Abs.1710).

In a phase II double-blind, randomized clinical trial, conducted at the University of Pittsburgh Medical Center (Pittsburgh, PA), involving 288 men with HRPC, responses to atrasentan were seen in a variety of clinical measures related to this indication, including TTP, the primary end-

point, and other measures such as time-to-PSA progression. The relationship between TTP and time-to-PSA progression was investigated in 244 patients with documented dates for TTP and/or time-to-PSA progression using a quartile method to determine if PSA results, expressed as time-to-PSA progression, correlate with TTP results. There was a positive association between TTP and time-to-PSA progression, with a similar association demonstrated regardless of treatment group (placebo and atrasentan). Time-to-PSA progression preceded TTP in 61/244 (66%) patients with a median time interval of 59 days between time-to-PSA progression and TTP for subjects with both dates documented (n=119). In conclusion, time to PSA progression is associated with TTP, with time-to-PSA progression usually preceding TTP, even in metastatic HRPC (Nelson JB, etal, ASCO03, Abs. 1642).

	TTP (days)				
Time to PSA progression (days)	**≤60**	**>60-128.5**	**>128.5-223**	**>223**	**Total**
≤34.5	34 (56%)	16 (26%)	8 (13%)	3 (5%)	61
>34.5-64	25 (41%)	13 (21%)	15 (25%)	8 (13%)	61
>64-127.5	3 (5%)	28 (46%)	18 (30%)	12 (20%)	61
>127.5	0	3 (5%)	21 (34%)	37 (61%)	61

Note: Percentages are reflective of subjects in each time-to-PSA progression quartile

In February 2003, a preliminary review was conducted by an Independent Data Monitoring Committee of an 810-patient, multinational, double blind placebo-controlled, phase III clinical trial (protocol IDs: ABBOTT-627, ABBOTT-M00-211, UCLA-010506301), initiated in May 2001 to examine the effect of atrasentan in men with advanced or metastatic HRPC. The trial objective was to determine TTP, efficacy and safety of daily oral ABT-627. Treatment resulted in improvements in development of bone pain as an adverse event, prostate-specific antigen (PSA) levels, and biochemical markers of skeletal progression in patients taking atrasentan versus placebo. However, the study did not meet its primary endpoint of TTP and, therefore, will be stopped.

This composite TTP endpoint, defined by clinically meaningful events, was developed and applied as the primary endpoint to the two large, randomized, placebo-controlled phase III clinical trials in prostate cancer, one (M00-211), in men with metastatic HRPC, and the other (M00-244), in men with rising PSA, but no objective metastases. These events, selected to correlate with a reduced QoL or necessitate a change of clinical management, include increase in pain requiring intervention, skeletal related events, such as compression fractures, other clinical events attributable to prostate cancer requiring intervention, such as urinary tract obstruction, bone-scan progression defined by appearance of new lesions, and CT progression defined by modified RECIST criteria. PSA progression was excluded. Blinded independent review of study endpoints was implemented to further reduce bias from PSA data and to ensure that the criteria defining progression are consistently applied across >200 investigative sites. Central, independent endpoint review includes evaluation of radiologic and clinical data by practicing clinicians. Accrual to these two trials with a placebo arm and an endpoint verification requirement has been rapid. Verification of complete endpoint data sets (including quality control, radiologic and clinical review) has taken 10 days on average. In order for delay in TTP to be a clinically meaningful endpoint, it must be precisely defined and carefully implemented (Humerickhouse R, etal, ASCO03, Abs. 724).

If a patient experienced disease progression by any of these criteria, he was considered to have completed the trial. The majority of patients who completed the trial did so within 3 months of starting treatment. These results in both the placebo and atrasentan arms are consistent with the rapid progression of bone disease in this end-stage patient population. In this trial, the mean change of PSA levels was 175 ngm/ml with atrasentan compared to 257 ngm/ml with placebo. Development of bone pain as an adverse event occurred in 24% of patients treated with atrasentan compared to 34% with placebo. Improvements in mean change of biochemical markers of skeletal progression were 27 IU/l of total alkaline phosphatase with atrasentan compared to 94 IU/L on placebo, and bone alkaline phosphatase was 9 IU/ml and 34 IU/ml, respectively. Atrasentan was well tolerated with a dropout rate lower than seen in the phase II clinical trial, and was comparable in patients treated with atrasentan versus placebo (10.8% versus 9.5%). The most common adverse events seen more frequently in patients treated with atrasentan compared to placebo, that were also consistent with phase II findings, were headache (14% versus 9%), peripheral edema (21% versus 7%), and rhinitis (19% versus 7%).

Patients completing the trial may continue treatment with atrasentan through an extension phase III clinical trial (protocol IDs: UCLA-0202002, ABBOTT-M00-258, NCI-G02-2110) if it is determined that they are benefiting from the drug. This open-label, multicenter phase III clinical trial to determine the safety of atrasentan in patients with HRPC, was initiated in October 2002 at UCLA's Jonsson Comprehensive Cancer Center with Robert Reiter, MD, as Study Chair. The trial will enroll approximately 1,400 patients. Oral atrasentan is administered once daily for 3 years in the absence of disease progression or unacceptable toxicity. Patients are followed at 1 month, and then every 3 months for 2 years. This trial is also enrolling patients from completed trials M00-211 or M00-244 who either progressed, or were actively treated when the double-blind treatment period ended.

A randomized, placebo-controlled, multicenter phase III clinical trial (protocol IDs: ABBOTT-M00-244, ABBOTT-ABT-627, UCLA-0107068) of atrasentan was initiated in November 2001 in the USA and Canada, to determine the efficacy and safety of this agent in patients with

nonmetastatic (Stage I, II or III) HRPC. Patients are randomized to one of two treatment arms. Patients in arm A are treated with daily oral atrasentan, while those in arm B are administered daily placebo. In both arms, treatment continues in the absence of disease progression. The trial objective is to determine the efficacy and safety of ABT-627. Approximately 900-1,000 patients will be accrued for this study. In February 2003, Abbott said it will continue this trial.

Bevacizumab

Bevacizumab (Avastin; Genentech), a chimeric monoclonal antibody (MAb), binds VEGF, and inhibits angiogenesis, resulting in antitumor activity in a number of human malignancies. Currently, Genentech is evaluating Avastin in a very aggressive program encompassing a variety of solid tumors, including phase III clinical trials in colorectal and breast cancer, and nonsquamous nsclc. As of June 2003, more than 2,000 patients had been treated with Avastin in clinical trials.

A most promising application involves combination regimens in advanced colorectal cancer. In June 2003, the FDA designated Avastin as a 'fast track' development program as first line treatment in patients with metastatic colorectal cancer, making it eligible for a rolling submission of a potential Biologics License Application (BLA). Genentech had submitted an application with the FDA for 'fast track' designation based on positive results from a randomized, active-controlled, multicenter, phase III clinical trial (protocol ID: GENENTECH-AVF2107g; UCLA-0008022) comparing the effectiveness of combination chemotherapy with bevacizumab with or without irinotecan, in treating chemotherapy-naive patients with metastatic colorectal cancer, that had been initiated in July 2000, and completed in October 2002.

The trial enrolled >900 patients who were stratified according to ECOG performance status, site of primary disease, and number of metastatic sites, and then randomized to 1 of 3 treatment arms. In arm A (n=403), patients were administered the Saltz regimen (IFL) consisting of IV irinotecan over 90 minutes, followed by IV leucovorin calcium over 1-2 minutes, and IV fluorouracil (5-FU) over 1-2 minutes, weekly for 4 weeks; IV placebo was administered over 30-90 minutes every other week. Courses were repeated every 6 weeks. In arm B (n=412), patients were treated with irinotecan, leucovorin calcium, and 5-FU as in arm A plus IV bevacizumab administered over 30-90 minutes every other week. Courses are repeated every 6 weeks. In arm C (n=110), patients were administered IV leucovorin calcium over 2 hours and IV 5-FU over 1-2 minutes beginning 1 hour after initiation of leucovorin calcium, weekly for 6 weeks, and IV bevacizumab, administered over 30-90 minutes, every other week.

Courses were repeated every 8 weeks. Treatment was continued in the absence of disease progression or unacceptable toxicity for a maximum of 16 courses in arms A and B. Arm C was discontinued once safety with the IFL regimen was established. Patients with progressive disease could continue treatment with another chemotherapy agent with or without bevacizumab. Patients in arm A with progressive disease may continue on another chemotherapy agent but could not be treated with bevacizumab. Patients in arm B with progressive disease could continue on bevacizumab alone or in combination with another chemotherapy agent. Patients in arm C with progressive disease could continue on bevacizumab alone or in combination with irinotecan, or possibly another chemotherapy agent. Patients are followed every 4 months for survival, which is the primary endpoint of this trial.

Grade 3 hypertension occurred in 10.9% of patients in arm B, compared to 2.5% in arm A. Grade 3 proteinurea occurred at a rate of 8% in both arms and bleeding occurred in 3.1% of patients in arm B and in 2.5% in arm A. Thromboembolism occurred in 19% of patients in arm B compared to 16.1% in arm A. In addition, GI perforation, an uncommon event, was limited to patients in arm B, and may be a direct effect of the addition of bevacizumab to chemotherapy.

This trial met its primary endpoint of improving overall survival. The overall survival data, as measured by a hazard ratio (HR), indicated that the chance for survival in patients treated with Avastin plus chemotherapy increased by 50% compared to those on chemotherapy alone, corresponding to an HR of 0.65. This benefit was stronger than anticipated, because the study was designed to detect a HR of 0.75, or a 33% increase in chance for survival. This benefit represents an extension in the MST of patients treated with Avastin plus chemotherapy by approximately 5 months from 15.6 months in patients treated with chemotherapy alone, to 20.3 months. Median TTP increased 71% from 6.2 months in the chemotherapy arm to 10.6 months in the Avastin plus chemotherapy arm. Avastin plus chemotherapy was also shown to improve overall response rates from 35% in the group treated with chemotherapy alone to 45% in that treated with Avastin plus chemotherapy. The duration of response increased from 7.1 months with chemotherapy to 10.4 months with Avastin plus chemotherapy.

Results of the randomized phase III clinical trial confirm those of a multicenter phase II clinical trial (protocol ID: E2200) of bevacizumab added to irinotecan, fluorouracil and leucovorin (IFL), as front line therapy in previously untreated patients with measurable advanced colorectal cancer. The first 20 patients were treated with CPT-11 (125 mg/m^2), 5-FU (500 mg/m^2) and LV (20 mg/m^2), weekly, for 4 of 6 weeks, and bevacizumab (10 mg/kg) every other week. Following a toxicity review of other trials using IFL, subsequent patients were enrolled at reduced starting doses of CPT-11 (100 mg/m^2) and 5-FU (400 mg/m^2). Among 92 patients accrued during a 12-month period, toxicity data are available for 83 (median 5 cycles; range=1-14). No statistically significant differences

in overall Grade 3 or Grade 4 toxicity were observed based on starting doses of IFL. No treatment related deaths occurred. Grade 3 diarrhea occurred in 15 patients with no Grade 4 diarrhea. Grade 3 or Grade 4 neutropenia occurred in 18 and 12 patients, respectively. Febrile neutropenia occurred in 4 patients. Among 45 bleeding events, 43 were Grade 1 and 23 were epistaxis. There was one Grade 4 epistaxis, requiring tamponade but no transfusion, and one Grade 3 melena. There were 9 thrombotic events, 4 Grade 3 (requiring anticoagulation), and 4 Grade 4 (pulmonary embolism). Proteinuria and hypertension were infrequent. With a median follow up of 7.6 months, confirmed responses by RECIST on 70 patients, include 2 (2.9%) CR and 30 (43%) PR, for an ORR of 45.7%. Therefore, bevacizumab plus IFL exhibits substantial activity in patients with advanced colorectal cancer (Giantonio BJ, etal, ASCO03, Abs.1024).

One of the early concerns with Avastin involved several serious side effects such as hemorrhage, thrombosis/embolism, hypertension, and proteinuria. Because of this fact, all phase III clinical trials being carried out by ECOG require an interim toxicity review by the ECOG data monitoring committee to proceed to full accrual. Among 519 patients treated with bevacizumab there were 3 bleeding related deaths, 2 from hemoptysis (E4599), and 1 CNS hemorrhage (E3200). Grade 3 and Grade 4 toxic events are tabulated below.

		Hemorrhage[1] (events/patient)		Thromboembolism /Embolism[1] (events/patient)		Hypertension[2] (events/patients with toxicity data)	
Protocol ID	**Regimen**	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**
E3200	Oxaliplatin, 5-FU, leucovorin + bevacizumab	3/160	1/160	1/160	0	6/75	1/75
	Oxaliplatin, 5-FU, leucovorin	1/160	0	2/160	1/160	1/73	0/73
	Bevacizumab	3/160	2/160	1/160	1/160	5/75	0/75
E4599	Carboplatin, paclitaxel + bevacizumab	1/60	0	0	1/60	3/54	0/54
	Carboplatin, paclitaxel	2/60	0	0	1/60	0/52	0/52
E2100	Paclitaxel + bevacizumab	0/50	0	1/50	0	0/10	0/10
	Paclitaxel	0/50	0	2/50	0	0/6	0/6
E2200	Irinotecan, 5-FU, leucovorin + bevacizumab	0/89	1/89	4/89	4/89	1/85	0/85

[1] *from ADEER reports*

[2] *from case report forms (CRF)*

Proteinuria was uncommon and never >Grade 2. Although a contribution of bevacizumab to the risk of hemorrhage and hypertension is suggested, the frequency of occurrence is low. The relationship to thromboembolic risk is not supported by the current phase III data, but merits continued monitoring (Gray R, etal, ASCO03, Abs 825).

The risk of hemorrhage first surfaced as a complication in a randomized phase II clinical trial evaluating carboplatin and paclitaxel +/- bevacizumab in chemotherapy-naive patients with advanced nsclc (DeVore RF, etal, ASCO00, Abs. 1896). Although MST ranged from 53 weeks to 76 weeks, sudden, life-threatening hemoptysis occurred in 6/66 patients treated with chemotherapy and bevacizumab; 4 episodes were fatal, all in patients with squamous cell histology. Squamous histology and bevacizumab therapy were the only factors associated with life threatening hemorrhage. Based on this observation, a randomized phase II/III clinical trial cancer (protocol ID: E-4599, CTSU) was initiated to compare the toxicity of paclitaxel and carboplatin with or without bevacizumab in patients with advanced, metastatic, or recurrent nonsquamous cell nsclc. A total of 640 patients will be accrued for this trial to be stratified according to measurable disease, prior radiotherapy, weight loss, disease stage (Stage IIIb versus Stage IV versus recurrent), and randomized to 1 of 2 treatment arms. Patients in arm A are administered IV paclitaxel over 3 hours followed by IV carboplatin over 15-30 minutes on day 1. Patients in arm B are administered paclitaxel and carboplatin as in arm A followed by IV bevacizumab over 30-90 minutes on day 1. Treatment in both arms is repeated every 3 weeks for up to 6 courses in the absence of disease progression or unacceptable toxicity. After completion of 6 courses, patients in arm B with stable or responding disease continue on bevacizumab only. Treatment is repeated every 3 weeks in the absence of disease progression or unacceptable toxicity. Patients are followed every 3 months for 2 years, every 6 months for 3 years, and then annually thereafter. Alan B. Sandler, MD, of ECOG is the PI.

A retrospective analysis was performed to determine what proportion of newly evaluated patients with advanced disease seen at Fox Chase Cancer Center (FCCC; Philadelphia, PA) were eligible for ECOG 4599 on the basis of eligibility criteria excluding performance status (PS) 2, CNS metastases, squamous histology, and/or therapeutic anticoagulation/NSAID, based on visits of patients to thoracic oncology (n=260) at FCCC scheduled with 6 medical oncologists from March 1, 2002 through August 8, 2002. There were 45 patients who were ineligible for this analysis because of tumor histology (mesothelioma=8, small-cell lung cancer=6, mixed histology=5, non-lung cancer=26). Of the remaining 215 patients with nsclc, 8 had incomplete charts for review; 7 had Stage I, 8 Stage II, and 43 Stage III nsclc. Of the remaining 150 patients, only 68 (45.6%) were eligible. Among 82 ineligible patients, 21 (25.6%) had PS>2, 20 (24.3%) had CNS metastases, 11 (13.4%) had squamous histology, 9 (10.9%) had therapeutic anticoagulation, and 21 (25.6%) had >2 criteria (PS/squamous histology=11, PS/CNS=3, PS/anticoagulation=2, CNS metastasis/anticoagulation=2, PS/squamous histology/anticoagulation=2, PS/squamous histology/CNS

metastasis=1). Only 35 of the 68 eligible patients were chemotherapy-naive, and only 6 of these (17%) enrolled in the trial. Based on the data reviewed, more than 50% of those who might otherwise have been eligible for standard advanced nsclc trials were not candidates for E4599. Outcome with respect to this study must be interpreted in the context of eligibility restrictions (Somer RA, etal, ASCO03, Abs. 2687).

Avastin is also being evaluated in combination with oxaliplatin. A phase III randomized clinical trial (protocol IDs: E-3200, CTSU) was initiated in November 2000, to compare response, TTP, and overall survival of patients with refractory advanced or metastatic colorectal adenocarcinoma, treated with oxaliplatin, 5-FU, and leucovorin (FOLFOX4) with or without bevacizumab versus bevacizumab alone. This trial was completed in April 2003. Patients are stratified according to ECOG performance status, measurable disease, and prior radiotherapy, and then randomized to 1 of 3 treatment arms.

A total of 693 patients (231 per treatment arm) who had been treated with a flouropyrimidine- and an irinotecan-based regimen used either alone or in combination, were accrued in this study. In arm A, patients were treated with IV bevacizumab (10 mg/kg) over 30-90 minutes and IV oxaliplatin (85 mg/m^2) over 2 hours, on day 1. IV leucovorin calcium (200 mg/m^2) was administered over 2 hours, and IV 5-FU (400 mg/m^2), followed by 5-FU (600 mg/m^2) by continuous infusion over 22 hours, on days 1 and 2. In arm B, patients were treated with the FOLFOX4 as in arm A, alone. In arm C, patients are administered bevacizumab monotherapy as in arm A. Treatment in all arms was repeated every 2 weeks in the absence of disease progression or unacceptable toxicity. Patients are followed every 3 months for 2 years, every 6 months for 3 years, and then annually thereafter. Bruce J. Giantonio, MD, of ECOG is Protocol Chair. Among 223 patients evaluable for toxicity (arm A=75, arm B=73, arm C=75), there were two deaths, both in arm A, one from CNS hemorrhage, and one from pulmonary failure.

Adverse Event	FOLFOX4+ bevacizumab		FOLFOX4		Bevacizumab	
	N=75		N=73		N=75	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade G4
Hemorrhage	3%	0	0	0	3%	0
Thrombosis/ embolism	4%	0	1%	0	1%	0
Hypertension	8%	1%	1%	0	7%	0
Neutropenia	n/a	8%	n/a	21%	0	0
Febrile neutropenia	1%	0	3%	0	0	0
Infection with neutropenia	0	1%	6%	1%	0	0
Diarrhea	11%	0	11%	0	1%	0
Vomiting	5%	0	1%	0	1%	0
Neuropathy (sensory)	4%	0	3%	0	0	0
Fatigue	8%	0	14%	1%	4%	1%
Worst grade	37%	11%	25%	23%	20%	9%

Overall, the rate of Grade 3 toxicities was 37% in arm A, 25% in arm B and 20% in arm C, and Grade 4 toxicity was 11% in arm A, 23% in arm B, and 9% in arm C. Addition of bevacizumab to FOLFOX4 did not substantially alter the latter's toxicity profile. Data also indicated that there is an association of bevacizumab with a low incidence of bleeding and hypertension, but an increased risk of thromboembolism is not evident. Also, chemotherapy-associated Grade 4 neutropenia may be reduced in patients treated with bevacizumab (Benson AB, etal, ASCO03, Abs. 975).

BMS-247550

BMS-247550 is a semisynthetic analog of epothilone B and one of a new class of cytotoxics with a mode of action similar to that of paclitaxel, i.e., microtubule stabilization, and an ability to overcome taxane resistance. BMS-247550 has shown activity against a variety of tumor types in phase I and II clinical trials.

A multicenter, randomized phase II clinical trial was conducted in various centers in the USA and Europe including the Catholic University (Leuven, Belgium), Centre Hospitalier General (Belfort Cedex, France), Vanderbilt University Medical Center (Nashville, TN), University of California Davis Cancer Center (Sacramento, CA), Hospital 12 de Octubre (Madrid, Spain), Rush Medical College (Chicago, IL), Institut Gustave Roussy, Instituto Nazionale per la Ricerca sul Cancro (Genoa, Italy), and Greenebaum Cancer Center (Baltimore, MD), in patients with Stage III/IV or recurrent metastatic nsclc who failed one prior platinum-containing regimen, using two different administration schedules of BMS-247550. To address neuropathy seen with the original 50 mg/m2 over 1-hour regimen (Delbaldo C, etal, ASCO02, Abs. 1211), the schedule was amended to a randomization to a 3-hour infusion of 40 mg/m^2 on day 1, or 1-hour infusion of 6 mg/m^2 on days 1-5. Cycles were repeated every 21 days. After 18 patients were treated at 40 mg/m^2, all subsequent patients were treated at 32 mg/m^2, because of frequency of mucositis and neutropenia.

Among 78 patients enrolled in arm A (32 mg/m^2) and administered BMS-247550 as a 3-hour infusion every 21 days, and 74 in arm B (6 mg/m^2) as a daily infusion for 5 consecutive days every 21 days, safety data is available on 76 patients in arm A and 69 patients in arm B. Regarding nonhematologic toxicities, there was only 1 (1%) case of Grade 4 sensory neuropathy in arm A. Grade 3 toxicities included 4 (5%) cases of fatigue, 1 (1%) case of myalgia, 2 (3%) of arthralgia, 2 (3%) of vomiting and 2 (6%) of sensory neuropathy in arm A, compared to 6 (9%) cases of fatigue, 1 (1%) case of myalgia, 3 (4%) of vomiting and 4 (6%) of sensory neuropathy, in arm B. Regarding hematologic malignancies, there were 11 (15%) cases of Grade 3 and 9 (12%) cases of Grade 4 neutropenia in arm A, compared to 4 (6%) and 6 (9%), respectively, in arm B. Grade 4 and Grade 3 febrile neutropenia occurred in 2 (3%) and 5 (7%), respectively in arm A, compared to 1 (1%) and 2 (3%),

respectively, in arm B. There was no Grade 4 thrombocytopenia; there were 2 (3%) cases of Grade 3 thrombocytopenia in arm A and 1 (2%) case in arm B. Only 2 (3%) patients discontinued treatment because of toxicity in arm A and 5 (7%) in arm B. There were 2 deaths in each arm. In arm A, there was 1 (1%) CR, 9 (12%) PR, and disease stabilized in 27 (36%) and progressed in 30 (39%); 9 (12%) patients could not be evaluated. In arm B, there was 1 (1%) CR, 6 (9%) PR, and disease stabilized in 21 (30%) and progressed in 28 (41%); 13 (19%) patients could not be evaluated. Among the 17 responders, 7 had been previously treated with a taxane. BMS-247550 was well tolerated and active when administered as either an intermittent or daily x 5 schedule to patients with advanced nsclc exposed to prior platinum-based regimens (Vansteenkiste JF, etal, ASCO03, Abs. 2519).

A multicenter trial (protocol ID: MSKCC-01064, MSKCC-01064A, NCI-3634) of BMS-247550 with or without estramustine phosphate in patients with progressive castrate-metastatic prostate cancer, was initiated in October 2001, and conducted in two parts. William K. Kelly, MD, of Memorial Sloan-Kettering Cancer Center (MSKCC) is Protocol Chair. Trial objectives are to determine MDT of BMS-247550 combined with estramustine in the phase I portion of the study, compare the safety and efficacy of BMS-247550 with or without estramustine in the phase II portion, and correlate the clinical outcomes with reverse transcriptase-polymerase chain reaction (RT-PCR)-based assay for PSA mRNA in patients treated with these regimens.

In phase I, IV BMS-247550 was administered over 1 hour on day 2, and oral estramustine 3 times daily on days 1-5. Treatment continued every 3 weeks in the absence of disease progression or unacceptable toxicity. Escalating doses of BMS-247550 were administered to cohorts of 3-6 patients until MTD was determined. In the dose-escalation phase I portion of this clinical trial, BMS-247550 with estramustine phosphate was administered to 9 chemotherapy-naive patients with progressive metastatic prostate cancer following castration. Escalating doses of BMS-247550 (35 to 40 mg/m^2) were administered IV with estramustine phosphate (280 mg) PO, thrice daily for 5 days every 21 days. At 35 mg/m^2, none of 3 patients treated showed Grade 3/4 toxicity. At 40 mg/mg^2, 3 of 6 patients experienced Grade 3/4 neutropenia and 1 patient Grade 3 nausea. There were no hypersensitivity reactions or other significant toxicity. A >50% post-therapy decline in PSA was observed in 5/5 evaluable patients. Soft tissue regression and bone metastasis improvement was also documented (Smaletz O, etal, ASCO02, Abs.732:184a). Preliminary results of this phase I trial established that BMS-247550 plus estramustine could be safely administered, and was clinically active with 11/12 (92%) evaluable patients showing a >50% post-therapy PSA decline.

The multicenter, randomized, phase II portion of this trial, being performed at MSKCC, University of San Francisco (UCSF), Dana-Farber Cancer Institute, and MDACC, was designed to determine the efficacy and toxicity profile of BMS-247550 with or without estramustine According to the protocol, chemotherapy-naïve patients with progressive castrate-metastatic prostate cancer and normal hepatic/renal function, are randomized to IV BMS-247550 (35 mg/m^2) infused over 3 hours, every 3 weeks (arm A), or BMS-247550 (as in arm A) on day 2 plus estramustine (280 mg) PO thrice daily on days 1 to 5, plus coumadin (2 mg), daily (arm B). The accrual goal is 46 patients per arm; however a 2-stage design with an early stopping rule has been applied so that further accrual in either arm will cease if >7 patients out of the first 22 enrolled do not achieve a >50% post-therapy PSA decline. Among 43 enrolled patients (arm A=21, arm B=22) there were no Grade 4 toxicities in either arm. Grade 3 neutropenia occurred in 3 patients in each arm, and Grade 3 neuropathy in 1 patient in arm A. Most other toxic side effects were Grade 1/2 neuropathy and neutropenia. Both arms fulfilled the requirements of the early stopping rule and accrual to both arms continues. BMS-247550 with and without estramustine is well tolerated with acceptable toxicity. Significant clinical activity had been observed with BMS-247550 alone, and in combination with estramustine. Randomized, phase III clinical trials will be needed to see if the addition of estramustine to BMS-247550 improves survival (Kelly WK, etal, ASC03, Abs.1584).

CeaVac

CeaVac, under development by Titan Pharmaceuticals (South San Francisco, CA), is a murine IgG1 anti-idiotype monoclonal antibody (MAb), generated against the 8019 IgG1 MAb that mimics CEA. CeaVac targets the CEA epitope and stimulates CEA-specific T cells and B cells. In 2003 Titan announced that it is no longer allocating internal resources to the development of CeaVac as part of a strategic plan to reduce expenditures.

Results from a multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial of CeaVac plus 5-FU/leucovorin (LV) in previously untreated Stage IV (Dukes' D) colorectal carcinoma, demonstrated a trend toward overall survival improvement of approximately 2 to 3 months in patients treated with >5 doses of CeaVac versus placebo (modified intent-to-treat population), but failed to demonstrate a statistically significant improvement in the primary endpoint of survival in the overall population evaluable for efficacy, or the intent-to-treat population. The trial, conducted at several locations in the UK, including City Hospital Nottingham, Leicester Royal Infirmary, North Middlesex Hospital, Guys Hospital London, and Royal Marsden Hospital (Sutton, UK), and in several USA locations, including Georgia Cancer Research Center (Decatur, GA) and Sidney Kimmel Cancer Center (San Diego, CA), was based on promising phase II results in patients with advanced colorectal cancer. Major endpoints were survival, TTP and anti-CEA immunity.

In this trial, patients were stratified by site of primary tumor (colon or rectum) and treatment location (USA or non-USA), and randomized 2:1 to be treated with CeaVac or placebo. Patients were treated with 2 mg CeaVac (or placebo) for 4 injections every 2 weeks and then monthly. 5-FU and LV (Mayo regimen) were administered concomitantly with CeaVac or placebo. From November 1998 to July 2001, 630 patients were randomized in the 2 arms that were well balanced for multiple prognostic factors at baseline. Patients were on study drug for a median of 31 weeks (31 for CeaVac and 28 for placebo) and were treated with a median of 5 cycles of 5-FU/LV. CeaVac was well tolerated with no significant increase in treatment-related adverse events. Antibodies to CEA were developed in >75% of patients treated with CeaVac, and survival correlated with the strength of immune response. There was no significant difference in MST or TTP for patients treated with CeaVac or placebo in the intent-to-treat analysis. Patients treated with a prospectively defined minimal priming regimen of CeaVac (6 doses) showed a trend towards improved survival versus placebo (19.1 versus 17.1 months), with strengthening of this trend for patients treated with 8 or more doses (21.3 versus 18.5 months). CeaVac was well tolerated and induced anti-CEA immunity in most patients (Bhatnagar A, etal, ASCO03, Abs. 1041).

CCI-779

CCI-779, under development by Wyeth, is a structural analog of the macrocyclic lactone sirolimus, previously called rapamycin, initially isolated from the soil bacteria *Streptomyces hygroscopicus*. CCI-779 is an immunophilin-binding antibiotic that blocks the initiation of the translation of mRNA by inhibiting mammalian target of rapamycin (mTOR).

Risk factor analysis, based on results from a randomized, double blind, phase II clinical trial, in which IV CCI-779 was administered as second line treatment to 105 patients with advanced RCC, suggests that CCI-779 prolongs survival in RCC. The trial evaluated 3 weekly dose levels, 25 mg, 75 mg, and 250 mg (Atkins MB, etal, ASCO02, Abs. 36:10a). Compared with results from a trial of first line interferon (IFN), administered to 437 patients with RCC (Motzer RJ, etal, J Clin Oncol, 1 Jan 2002;20(1):289-96), MST was 19.3 months with CCI-779 compared to 13.8 moths with IFN in the intermediate risk group, and 8.2 months compared to 4.9 months in the high risk group, respectively. Despite limitations of a nonrandomized comparison, and the different patient populations involved, CCI-779 appears to confer a survival advantage in patients with RCC classified as intermediate and poor risk compared to IFN-treated patients in these risk groups (Hidalgo M, etal, ASCO03, Abs. 804).

Cetuximab

Cetuximab (Erbitux; ImClone) is an investigational IgG1 MAb that targets the epidermal growth factor receptor (EGFr) and blocks the ability of EGF to initiate receptor activation and signaling to the tumor. It is believed that this blockade results in an inhibition of tumor growth by interfering with the effects of EGFr activation including tumor invasion and metastases, cell repair and angiogenesis. EGFr, when expressed by tumors, usually results in aggressive disease progression, poor response to traditional therapy, and poor survival. Because cetuximab can shrink tumors, and has fewer side effects than standard cytotoxic drugs when used alone, it may be appropriate both as combination therapy and as a monotherapy, especially in patients who would not be able to tolerate further standard chemotherapy.

Cetuximab is being evaluated in several clinical trials in a variety of solid tumors including head and neck, ovarian, pancreatic and non-small lung cancer, with special emphasis in colorectal cancer. Because cetuximab blocks the EGFr, thereby inhibiting the abnormal growth of cancer cells, patients whose colorectal tumors overexpress EGFr are likely to benefit from cetuximab. It is for this indication that ImClone Systems (New York, NY), and its partners, Bristol-Myers Squibb in the USA and Merck KGaA in Europe, are pursuing approval as third line treatment of metastatic colorectal cancer, either alone or in combination with irinotecan.

In August 2003, ImClone submitted a BLA to the FDA for the approval of Erbitux, in combination with irinotecan, for the treatment of patients with EGFr-expressing irinotecan-refractory metastatic colorectal cancer. ImClone has also requested priority review of the application and accelerated approval consideration. In June 2003, Merck KGaA filed marketing authorization applications (MAA) with the European Agency for the Evaluation of Medicinal Products (EMEA), and with Swissmedic for Erbitux for the indication of metastatic colorectal cancer as a monotherapy, and in combination with irinotecan. If successful, Merck could bring the cancer drug to market in Switzerland as soon as late 2003, because the Swiss authority has determined that cetuximab is suitable for an accelerated registration procedure. Marketing authorization across the European Union is expected in 2004. Merck licensed the right to market cetuximab outside of the USA and Canada and the co-exclusive right to market cetuximab in Japan, from ImClone, in 1998.

Filings are based on results reported at ASCO03, from the European phase II clinical trial (protocol ID: 007) in colorectal cancer, referred to as the Bowel Oncology With Cetuximab Antibody (BOND) trial. In this trial, cetuximab, when used in combination with irinotecan, represented a significant advance in the treatment of patients with metastatic colorectal cancer, slowing progression of the disease by more than 4 months, and shrinking tumors by 50% or more in 22.9% of patients; overall, disease stabilized or improved in half of all patients treated with the combination regimen. MST for patients with advanced stage disease, treated with the combination therapy, was

8.6 months, with approximately one third of the 329 patients enrolled in the trial being alive after one year.

The BOND trial was designed to compare cetuximab alone as monotherapy, and in combination with irinotecan, in 329 patients with metastatic colorectal cancer expressing EGFr whose disease had ceased to respond to chemotherapy. Two thirds of the patients were administered cetuximab and irinotecan while one third was treated with cetuximab monotherapy. Data from the BOND study indicate that cetuximab monotherapy results in an overall response rate of 11%. When administered in combination with irinotecan, a statistically significant improvement in efficacy is observed, compared with cetuximab alone, with an overall response rate of 22.9%. The study demonstrates that a combination of cetuximab and irinotecan is beneficial even when patients have ceased to respond to irinotecan.

This multicenter, randomized, phase II clinical trial, initiated in Europe in September 2001, was completed in December 2002. Secondary endpoints included TTP and survival time. Among 576 patients screened, 470 (82%) were EGFr-positive and 329 of these patients were randomized in a 2:1 ratio. Patients in arm A were treated with cetuximab, administered as a slow IV infusion over approximately one hour, first as a 400 mg/m^2 infusion, and then as a weekly 250 mg/m^2 infusion, plus irinotecan at the same dose and schedule on which they had been progressing. Patients in arm B were treated with cetuximab monotherapy with the option to switch to the combination regimen after failure of cetuximab monotherapy.

In terms of toxicity, patients treated with the combination of cetuximab and irinotecan experienced severe side effects, primarily related to irinotecan therapy. Among 218 patients accrued in arm A, and 111 in arm B, there were 211 serious adverse events; 65 (31%) were considered at least possibly related to the study medication, but were consistent with the known safety profiles of irinotecan and cetuximab. The most frequent Grade 3 or 4 events in patients treated with the combination regimen were diarrhea (21.2%), weakness (13.7%), low white blood cell count (13.7%) or vomiting (6.1%). Patients treated with cetuximab monotherapy experienced fewer side effects; 13 % experienced difficulty breathing, 10.4% weakness, and 5.2% abdominal pain. Approximately 50% of patients in the BOND trial developed a mild-to-moderate rash as a side effect of the treatment. The rash resolved itself spontaneously in most patients, and was not considered to be a serious problem. Severe allergic reactions in BOND have been reported in 4 out of 329 patients. Preliminary safety evaluation is based on investigator assessment. Response rate in arm A was 17.9 % and median TTP was 126 days. Response rate in arm B was 9.9 % and median TTP was 45 days (Cunningham D, etal, ASC003, Abs. 1012).

Centers participating in the BOND trial, include Royal Marsden Hospital, St. Luc University Hospital (Brussels, Belgium), Ospedale Niguarda Ca' Granda (Milan, Italy), Hospital Pitie-Salpetriere (Paris, France), Institut Jules-Bordet (Brussels, Belgium), Istituto Clinico Humanitas (Rozzano, Italy), and University Hospital Gasthuisberg (Leuven, Belgium), among others. David Cunningham, MD, head of the gastrointestinal and lymphoma units at the Royal Marsden Hospital in London and Surrey, UK was the lead investigator of the BOND trial.

The BOND trial design carefully took into consideration the controversy of the previous randomized clinical trial in the same setting, that resulted in the FDA's refusal to accept the trial's conclusions. In that trial, the time between irinotecan failure and the initiation of cetuximab had been too long and, therefore, could have contributed to resensitization to irinotecan of previously considered resistant tumors thus inflating the response of cetuximab. In the BOND trial this interval was short.

Gefitinib

Gefitinib (Iressa; AstraZeneca) is a quinazoline-derivative that selectively and reversibly inhibits EGFr tyrosine kinase (EGFr-TK)-mediated intracellular signaling pathways. Iressa (250 mg), administered once daily for the treatment of inoperable or recurrent non-small-cell lung cancer (nsclc), was approved in July 2002 by the Japanese Ministry of Health, Labour and Welfare (MHLW), making Japan the first country worldwide to license the drug. Subsequently, Iressa was granted accelerated approval by the FDA in May 2003, for treatment of advanced nsclc, based on results from phase II clinical trials, conducted in the USA, showing a 13.6% PR rate among patients with progressive disease following failure of both platinum- and docetaxel-based chemotherapy regimens. Most responses with Iressa were seen in the first 8 weeks of treatment. As part of the FDA accelerated (or sub part H) approval process, AstraZeneca has agreed to complete a phase IV clinical trial program, designed to further demonstrate the clinical benefits of Iressa and satisfy FDA requirements for full approval. In May 2003, Iressa was also approved in Australia.

In February 2003, AstraZeneca submitted in Europe an MAA for Iressa for the treatment of locally advanced or metastatic nsclc in patients refractory to platinum-based and docetaxel chemotherapy. Submission for Iressa in Europe is based on data from two phase II trials, IDEAL 1 and IDEAL 2 (Iressa Dose Evaluation in Advanced Lung Cancer). These data confirmed that daily Iressa (250 mg) monotherapy provides clinically significant antitumor activity in patients with previously treated advanced nsclc. Final results from these trials were presented internationally in September 2002.

Although results from IDEAL 1 and IDEAL 2 indicated that Iressa exhibited a favorable safety profile, with the majority of side effects (diarrhea and skin rash) mild and reversible, in December 2002, the Japanese authorities reported incidence of interstitial lung disease (ILD), such as

interstitial pneumonia, pneumonitis and alveolitis. Cases of ILD have been observed in approximately 1% of patients treated with Iressa, with approximately 1/3 of the cases resulting in death. The reported incidence of ILD was about 2% in the Japanese post-marketing experience, about 0.3% in approximately 23,000 patients treated with Iressa in a USA expanded access program, and about 1% in the studies of first line use in nsclc (but with similar rates in both treatment and placebo groups). Patients present with acute onset of dyspnea, sometimes associated with cough or low-grade fever, often becoming severe within a short time and requiring hospitalization. ILD has occurred in patients treated with Iressa, previously exposed to radiation therapy (31% of reported cases), chemotherapy (57%), and no previous therapy (12%). Because Iressa is used as third line treatment in severely ill patients in late stages of their disease, even a high death toll (about 0.7%) did not preclude approval, but it may adversely affect Iressa's use in this target patient population.

One of the disappointments in Iressa's evaluation in advanced nsclc came when it showed no benefit in two large clinical trials, INTACT ('Iressa' NSCLC Trials Assessing Combination Treatment) 1 and 2, conducted in 2,130 chemotherapy-naïve patients with Stage III or IV nsclc. In this first line setting patients were randomized to Iressa 250 mg daily, Iressa 500 mg daily, or placebo, in combination with 6 cycles of platinum-based chemotherapy regimens, either gemcitabine and cisplatin (n=1093), or carboplatin and paclitaxel (n=1037). Adding Iressa to these cytotoxic regimens did not demonstrate any increase, or trend toward such an increase, in tumor response rates, TTP, or overall survival. Therefore, its unlikely Iressa will advance to an earlier treatment setting in the nsclc indication, unless of course it is shown to be effective in other combination regimens.

A multivariate analysis of 8 prespecified prognostic factors at trial entry, i.e., Stage III versus IV disease; PS 0/1 versus 2; weight loss in prior 6 months <5% versus >5%; gender; adenocarcinoma (including bronchoalveolar) versus other types (squamous or large cell or unspecified); and overall survival of patients with advanced nsclc treated with Iressa, in combination with platinum-based chemotherapy, in INTACT 1 and 2 clinical trials with presence versus absence of bone, brain, or liver metastases, was performed independently on each trial to assess which variables were predictive of improved survival. Significant factors for worse survival outcome in both trials were PS 2, weight loss, and bone and liver metastases; survival differences for gender and brain metastases were noted in INTACT 2. However, gender in particular was not consistently identified as an important factor in predicting survival outcome. Multivariate analyses of INTACT data did not show any consistent and demonstrable effects of gefitinib combined with chemotherapy on known prognostic factors for survival outcome, and did not reveal any new factors, in advanced nsclc (Giaccone G, etal, ASCO03, Abs. 2522).

However, researchers found that recurrence of lung tumors was slowed in patients who used Iressa as maintenance therapy following chemotherapy compared to those who did not use the agent at all or used it for <3 months. In examining data from the INTACT 2 trial, with the largest accrual, investigators found a trend toward improved survival in patients treated with Iressa (250 mg) of ≥90 days. Therefore, Iressa may be effective as a cytostatic agent to prevent growth and development of malignant cells and maintain tumor regression following chemotherapy. Interestingly, this maintenance effect was not seen in INTACT 1. Several studies are now in development in an attempt to validate these findings. Also, tissue samples are being analyzed for EGFr expression and its correlation with survival (Herbst RS, etal, ASCO03, Abs. 2523).

The observation that Iressa might keep cancer cells dormant for a period of time may result in a new opportunity for the drug as maintenance therapy. However, because the combination therapy results with Iressa were disappointing, it would still be necessary to seek other ways to improve response rates before maintenance therapy makes sense. More than >50% of patients with advanced nsclc never respond to initial chemotherapy.

Irofulven

Irofulven, under development by MGI Pharma (Bloomington, MN), is a semisynthetic analog of illudin S, a sesquiterpene isolated from the Jack o' lantern mushroom, *Omphalotus illudens*.

In April 2001, a multinational, randomized, phase II clinical trial was undertaken at UCLC Saint-Luc (Brussels, Belgium), CHU (Poitiers, France), Institut Gustave Roussy, Centre Val d'Aurelle (Montpellier, France), Hôpital Tenon (Paris, France), CHU (Kremlin-Bicetre, France), Hospital Aleman (Buenos Aires, Argentina), and CAC (Kremlin-Bicetre, France), among others, to investigate irofulven with or without prednisone in refractory (1-3 prior hormone therapy regimens) HRPC. The first 18 patients were treated with a dose of 24 mg/m^2, which was amended to 0.55 mg/kg in August 2001 in the subsequent 43 patients. IV irofulven was administered as a 30-minute infusion, on days 1 and 15, every 4 weeks either alone (arm A) or with 10 mg daily prednisone (arm B). The primary objective was PSA-based response rate.

A total of 61 patients (arm A=29, arm B=32) were randomized and treated with 142 cycles (median=2 per patient, range=1-6), with 2 patients still on treatment in November 2002; 30 patients had been treated with prior chemotherapy. Among 56 patients (arm A=28 and arm B=28; 5 patients <2 cycles) evaluable for response, there was confirmed PSA response in 8 patients (14%), 3 patients in arm A and 5 patients in arm B. There were 2 CR, 1 in a chemoresistant patient and 1 in a chemosensitive patient, and PSA levels stabilized in 11 patients with previously rising levels (3 patients with unconfirmed response). In 11 patients with measurable disease, there

were 2 PR (18%) 1 each in arm A and arm B), and disease stabilized in 8 (73%).

Among 61 patients evaluable for toxicity, principal adverse events were Grade 3 thrombocytopenia (13% of patients), Grade 3 (10%) or Grade 4 (2%) neutropenia, and Grade 3 visual disturbances (8%; 17% with the initial dose and 5% with the amended dose). Other adverse events consisted of Grade 3 vomiting (7%) and asthenia (3%) and Grade 3/4 anemia (7%). Treatment discontinuation for toxicity was required in 13 patients. No difference in the safety or efficacy profile between treatment arms was elicited. Therefore, irofulven demonstrates antitumor activity in HRPC when administered on the every other week dosing schedule (Tombal B, etal, ASCO03, Abs. 1636).

LY900003

LY900003 (Affinitak; Isis Pharmaceuticals) is a 20-mer phosphorothioate antisense oligonucleotide that inhibits protein kinase C alpha (PKC-α) isoform gene expression via an RNase H-mediated mechanism. Affinitak is in development under an alliance between Eli Lilly and Isis Pharmaceuticals (Carlsbad, CA).

A multinational, randomized phase III clinical trial (protocol ID: ISIS-3521-CS17) of chemotherapy and LY900003 (ISIS 3521) in previously untreated patients with advanced nsclc (Stage IIIb with malignant pleural/pericardial effusion or Stage IV), was initiated at Massachusetts General Hospital DanaFarber Partners CancerCare (Boston, MA), US Oncology (Houston, TX), Princess Royal Hospital (Hull, UK), CACF Baclesse (Caen, France), and Krankenhaus Grosshandorf in Germany, and Stanford University (Palo Alto, CA), based on results from a phase II trial of LY900003 in combination with carboplatin plus paclitaxel chemotherapy in advanced nsclc that produced a 48% response rate, with stable disease seen in an additional 35%, and a 15.9 month MST (Yuen A, etal, ASCO01, Abs. 1234:309a).

The primary endpoint of the phase III clinical trial was survival with a trial size sufficient to detect a 33% improvement in overall survival (MST from 8 to 10.9 months) with 80% power. From October 2000 to January 2002, 616 patients were randomized to one of two treatments, administered every 21 days. In arm A, LY900003 (2 mg/kg) was infused by continuous IV on days 1 through 14, with carboplatin (AUC=6) and paclitaxel (175 mg/m^2) administered as a 3-hour infusion on day 4, while in arm B, carboplatin and paclitaxel were administered as in arm A but without LY900003. Among all randomized patients, 57% had adenocarcinoma, and 87% Stage IV disease (Lynch TJ, etal, ASCO03, Abs. 2504).

In March 2003, it was reported that there was no difference in a primary log-rank analysis of the overall survival of the two groups, which was the primary endpoint of the study. MST of patients on LY900003 in combination with the carboplatin and paclitaxel regimen, was 10 months, compared to 9.7 months for those on chemotherapy alone. MST of the control group was longer than expected, in light of the fact that treatment groups in the trial were comparable with regard to all major prognostic factors. For example, each group had approximately 87% of patients with Stage IV disease and was comparable in terms of types of lung cancer. Using a stratified log-rank statistical analysis that considered predefined variables, including duration of treatment, based on all 616 patients in the study, survival of the LY900003-treated patients was greater than that of the patients in the control arm, and this result was statistically significant and merits further evaluation. In a survival analysis of the 256 patients who completed the prescribed course of 6 cycles of chemotherapy, MST was 17.4 months in those treated with LY900003 versus 14.3 months for patients on chemotherapy alone. Additionally, in the 256 patients completing the prescribed course of chemotherapy, results favored the LY900003 group across multiple secondary endpoints.

Addition of LY900003 to carboplatin and paclitaxel was well tolerated. There were no increases in severe toxicities or toxicity-related deaths in patients on LY900003, compared to those on chemotherapy alone. The most common side effects were fatigue and nausea. Patients on LY900003 in combination with chemotherapy experienced a higher rate of moderate thrombocytopenia, nausea and vomiting. Furthermore, because LY900003 is administered by continuous intravenous infusion, LY900003-treated patients had a higher incidence of catheter-related infections.

In February 2003, a second randomized, open-label, multicenter, phase III clinical trial (protocol IDs: UCLA-0210072, LILLY-H7X-MC-JVAA) was initiated by Eli Lilly in chemotherapy-naive patients with Stage IIIb or IV nsclc, to compare overall survival rate, PFS rate, TTP, tumor response rate and duration of response, and toxic effects of a regimen of gemcitabine and cisplatin with or without LY900003. According to the protocol, patients are stratified according to history of brain metastases (yes versus no), disease stage (Stage IIIb versus Stage IV), ECOG performance status (0 versus 1), and investigational center. Patients are randomized to 1 of 2 treatment arms. In arm A, patients are treated with gemcitabine IV over 30 minutes on days 1 and 8 and cisplatin IV on day 1. In arm B, patients are treated as in arm I plus LY900003 IV continuously on days 1-14. Treatment in both arms repeats every 21 days for up to 6 courses in the absence of disease progression or unacceptable toxicity. Patients who achieve CR after 6 courses may be treated with 2 additional courses after documentation of CR. Patients who achieve PR between courses 4 and 6 are being treated with additional courses, 2 courses at a time, at the discretion of the investigator. Patients are followed at 30 days, and at 2, 4, 6, 9, and 12 months or until disease progression, and then every 3 months thereafter.

Approximately 700 patients (350 per treatment arm) will be accrued for this study within 15 months. Diane

Prager, MD, at the Jonsson Comprehensive Cancer Center, at UCLA, is Protocol Chair.

Pemetrexed

Pemetrexed (Alimta; Lilly) is a multitargeted antifolate (MTA) that inhibits at least three enzymes, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), involved in folate metabolism and DNA synthesis.

In the USA, Alimta is in the process of a rolling submission to the FDA for use, with cisplatin, in the treatment of malignant pleural mesothelioma (MPM), based on results from the largest randomized clinical trial conducted in MPM. The trial's endpoints were survival, tumor response, and quality of life (QoL). In addition, in cooperation with the FDA, Lilly has provided Alimta free-of-charge to more than 600 patients with MPM as part of an expanded access, or compassionate use, program. Similar programs are underway in other countries around the world as well.

This multinational, randomized, phase III clinical trial (MSKCC-99085, CWRU-LILY-1599, LILLY-H3E-MC-JMCH(a), NCI-G00-1767) of 448 patients with malignant pleural mesothelioma (MPM) was initiated at the University of Virginia (Charlottesville, VA), Sydney Cancer Centre, Royal Prince Alfred Hospital (Camperdown, Australia), Prince Charles Hospital (Chermside, Australia), Hospital '12 de Octubre (Madrid, Spain), and University of Chicago (Chicago, IL), among others, to assess the efficacy of pemetrexed in combination with cisplatin on overall survival and QoL. Among 448 patients (Stage III/IV=77%) from 19 countries entering the study, 226 patients were administered pemetrexed in combination with cisplatin, and 222 were administered cisplatin only.

All comparisons favored the pemetrexed plus cisplatin arm. MST of patients on pemetrexed and cisplatin was 12.1 months, compared to 9.3 months for those on cisplatin alone, corresponding to an MST increase of 30%. Furthermore, the quality of life was significantly improved for patients treated with pemetrexed and cisplatin who reported significantly fewer symptoms including pain (53% at baseline), difficulty breathing (65%), fatigue (72%), anorexia (58%), and cough (35%). Common side effects of the treatment include neutropenia, diarrhea, and painful mouth ulcers. However, the rate of serious infection was low. The severity of neutropenia, as well as other side effects, was significantly ameliorated by folic acid and vitamin B12 supplementation (Gralla RJ, etal, ASCO03, Abs. 2496).

Additional analyses of the results of this randomized phase III clinical trial comparing cisplatin with or without pemetrexed in MPM, were undertaken. One such analysis was carried out to determine the correlation of pulmonary function tests with best tumor response status. This post-trial study considered whether pulmonary function tests are a more sensitive indicator of response to treatment than tumor response status, because tumor grows contiguously along the pleural surface. Lung function was assessed (adjusted for sex, age, and height) for slow vital capacity (SVC), forced vital capacity (PVC), and forced expiratory volume in one second (FEV1). Changes in these parameters all correlated significantly with tumor response status. In addition, pulmonary function tests were consistently better in responders than in patients with stable disease, and patients with stable disease had better pulmonary function tests than those with progressive disease (Paoletti P, etal, ASCO03, Abs. 2651).

	SVC (%)		FVC (%)		FEV1 (%)	
Outcome	Patients (#)	LS* Mean	Patients (#)	LS* Mean	Patients (#)	LS* Mean
Response	96	8.97	109	10.69	114	10.17
Stable disease	130	3.36	147	3.26	150	3.20
Progressive Disease	56	-2.78	65	-3.99	67	-6.03

**Least square*

Another inquiry into this randomized phase III clinical trial, conducted using multiple regression analysis, indicated that pemetrexed, in combination with cisplatin, offered a significant survival advantage over cisplatin alone. Both arms were supplemented with folic acid and vitamin B12. By applying Cox multiple regression analysis, it has been possible to identify additional factors other than treatment intervention that have affected survival. Various baseline factors assessed from 434 patients included vitamin supplementation, age, gender, geography, race, performance status, disease stage, histological subtype, time from diagnosis, white blood count (WBC), prior radiotherapy, homocysteine, methylmalonic acid, and cystathionine. All baseline factors were well balanced between treatment groups. Multiple regression analysis supported the finding that pemetrexed, in combination with cisplatin, does confer a superior survival advantage compared to cisplatin alone. Increased survival was also correlated with vitamin supplementation, good performance status, early disease stage, and epithelial subtype. Decreased survival was associated with WBC and cystathionine (Symanowski JT, et al, ASCO03, Abs. 2602).

QoL was a secondary endpoint of this randomized phase III clinical trial. Over the course of the trial, evaluations were collected weekly from all participating centers; initial and follow-up data were available for 96% of patients. This extremely high questionnaire completion rate rendered this a very powerful study. In gathering QoL data, investigators used an instrument known as the LCSS-Meso Scale, which is based on the Lung Cancer Symptom Scale (LCSS), a validated and widely used instrument for measuring QoL in patients with lung cancer. In addition to rating their overall level of QoL, patients were also asked to rate five specific symptoms associated with their disease, such as pain, shortness of breath, fatigue, appetite loss, and cough. About 93% of these patients were symptomatic at

trial entry, with at least 90% having at least three of these symptoms.

Differences in QoL parameters began at 6 to 9 weeks with the combination, despite the fact that there were no improvement in survival data at this point. After 18 weeks of therapy, at which point survival was significantly improved in the pemetrexed arm, significant improvements were seen with the combination in all thoracic parameters, as well as in fatigue, anorexia, and level of activity. These improvements were also significant in the summary evaluation completed by the patients at trial completion. Patients reported that the extent of their pain, shortness of breath and cough was significantly better by week 12, after 4 cycles of treatment with the combination regimen, compared to cisplatin alone.

These improvements persisted through two other measured periods of time, week 15 (5 cycles of treatment) and week 18 (6 cycles of treatment). In this study, evaluation was completed at the end of week 18. Patients' level of fatigue was significantly better by week 15, and lasted through week 18. By week 18, significantly more patients on the combination arm reported better QoL compared to patients on cisplatin only. As with the findings on survival, these results reached the level of statistical significance. Symptoms of pain, dyspnea, and cough were significantly improved even before the general symptoms of fatigue, anorexia, and activity, indicating that these symptoms arose from the local cancer, and were not necessarily attributable to metastatic disease. Improvement in the global measure of QoL was present at 12 weeks, and was significant by 18 weeks.

Differentiation in QoL and symptoms occurred rapidly (within first 3 cycles of the 21-day treatment cycle), reaching statistical significance in most parameters by week 15. All comparisons, regardless of level of significance, favored the combination arm. Therefore, in addition to survival advantage, the pemetrexed plus cisplatin regimen is associated with significant sustained improvement in QoL and symptom relief when compared with cisplatin alone (Gralla RJ, ASCO03, Abs. 2496). However, it is still not clear if QoL predicts survival, i.e. if higher QoL is also associated with longer survival.

Of course, treatment came with its own symptomatology. The most common side effect of the combination therapy was a decrease in white blood cell counts signaling neutropenia. However, the rate of serious infection was very low. The severity of neutropenia, as well as other side effects, including diarrhea and painful mouth ulcers, was significantly ameliorated by folic acid and vitamin B12 supplementation.

Folic acid (FA) and vitamin B12 (B12) were added to both treatment arms after December 1999, when a multiple regression analysis identified increased plasma homocysteine, and to a lesser extent, methylmalonic acid as predictive of increased risk of severe toxicity. Relative risk (RR) of select toxicities was assessed between all randomized and treated patients (n=448), and the supplemented with FA/B12 group (n=331). RR was also assessed between treatment arms within each group, as shown below. As expected, the pemetrexed and cisplatin combination arm resulted in greater incidence of serious adverse events and Grade 3/4 neutropenia, nausea and vomiting compared to cisplatin alone. Supplementation with FA and B12 reduced the incidence of these toxicities and the RR of toxicity between the two groups. The survival advantage in patients treated with the combination was maintained when FA/B12 was added. Therefore, the combination of pemetrexed and cisplatin, supplemented with FA/B12, should be considered the treatment of choice in MPM (Vogelzang NJ, etal, ASCO3, Abs. 2644).

	Randomized and Treated (n=448)		Supplemented with FA/B12 (n=331)		Relative Risk (FA/B12)/ Relative Risk (All treated)
	Pemetrexed + Cisplatin (n=226)	Cisplatin Alone (n=222)	Pemetrexed + Cisplatin (n=168)	Cisplatin Alone (n=163)	
MST (months)	12.1	9.3	13.3	10.0	
Hazard ratio (HR)	.77		.75		
Drug-related Serious Adverse Events	51	16	35	15	0.72
Relative Risk*	3.13		2.26		
Grade 3/4 Neutropenia	63	5	39	5	0.61
Relative Risk*	12.38		7.57		
Grade 3/4 Nausea	33	14	20	9	0.93
Relative Risk*	2.32		2.16		
Grade 3/4 Vomiting	30	8	18	7	0.68
Relative Risk*	3.68		2.49		

**Between arm comparison*

In April 2003, the Ireland Cancer Center (Cleveland, OH) initiated a multicenter, open-label, phase II clinical trial (CWRU-LILY-1502, LILLY-H3E-US-JMFZ) of pemetrexed disodium and gemcitabine in chemotherapy-naïve patients with advanced malignant mesothelioma, epithelial mesothelioma, and sarcomatous mesothelioma. Themajor objectives of this study are to determine the tumor response rate and overall survival as well as time to objective tumor response, duration of response, and toxicities of this regimen. This study will accrue 18 to 73 patients with a minimum life expectancy of 3 months and no known or suspected brain metastases. According to the protocol, patients will be administered gemcitabine IV over 30 minutes on days 1 and 8, and pemetrexed disodium IV over 8 to 15 minutes on day 8. Treatment repeats every 21 days for at least 6 cycles in the absence of disease progression or DLT. Patients will be followed at first after 30 days, then every 3 months.

A multicenter, randomized, phase III clinical trial comparing the combination of pemetrexed and docetaxel (Taxotere; Aventis) to docetaxel monotherapy in refractory advanced nsclc, was conducted at Indiana University (Indianapolis, IN), Princess Margaret Hospital (Toronto, Canada), Hospital Germans Trias (Pujol, Badalona, Spain), Instituto Arnaldo Vieira de Carvalho (San Paulo, Brazil), Pneumological Hosp 'C Forlanini' (Rome, Italy), MDACC, and the University of Colorado. Between March 2001 and February 2002, the trial enrolled 571 patients with recurrent nsclc (Stage IV=75% and Stage III=25%), previously treated with chemotherapy (95% had 1 prior chemotherapy regimen, and 5% 2 regimens; 90% had prior platinum therapy and 28% a taxane-based regimen). Trial objectives are assessment of overall survival, as well as, time to event measures, response rate, toxicity, and QoL.

Among the 571 patients, 283 were administered pemetrexed (500 mg/m^2) by IV infusion supplemented with vitamin B12 injections and folic acid, and 288 docetaxel (75 mg/m^2) by IV infusion, both on day 1 of a 21-day cycle. Grade 3/4 toxicities included neutropenia (40%), neutropenic fever (7%), anemia (6%), thrombocytopenia (2%), fatigue (5%), nausea (2%), anorexia (2%), diarrhea (1%), neuropathy(1%) and hypersensitivity (<1%). However, incidence of severe neutropenia, neutropenic fever, subsequent hospitalizations, and drug-related serious adverse events were significantly reduced in patients treated with pemetrexed. Documented infection was reported in 3% of the patients on docetaxel, and none of those on pemetrexed. Furthermore, incidence of Grade 3/4 alanine transaminase (ALT) was short-lived in the pemetrexed arm (Hanna NH, etal, ASCO03, Abs. 2503).

Mature results from this trial, presented at ASCO03, indicated that while the survival advantage, the primary endpoint of both arms of the study, was similar, pemetrexed was associated with fewer side effects. MST of patients on pemetrexed was 8.3 months, and 7.9 months for those on docetaxel. The probability of surviving one year was 29.7% in both arms. Incidence of severe neutropenia was 5% in the pemetrexed arm and 40% in the docetaxel arm, a difference that was statistically significant. The difference in the incidence of neutropenic fever, and subsequent hospitalizations between the pemetrexed and docetaxel arms, that was 2% in patients on pemetrexed compared to 13% in those on docetaxel, was also statistically significant. Another finding that reached statistical significance, i.e., the incidence of drug-related serious adverse events, including side effects that could lead to a life-threatening outcome, death or hospitalization, was 10% in patients on pemetrexed compared to 24% in those on docetaxel. Incidence of Grades 3/4 alanine transaminase (ALT), a laboratory measurement of liver function, was 1.9%, a rate that was significantly greater in the pemetrexed than in the docetaxel arm, but was transient.

A randomized, multicenter phase II clinical trial comparing pemetrexed, in combination with either carboplatin or oxaliplatin, was conducted to determine the response rate as well as time to event measures and toxicity, in patients with advanced nsclc. The trial, conducted at the University of Turin (Torino, Italy), St. Hildegardis (Mainz, Germany), Hospital 12 de Octubre, Newcastle General Hospital (Newcastle Upon Tyne, UK), Western General Hospital (Edinburgh, UK), Hospital Germans Trias i Pujol (Barcelona, Spain), ThoraxKlinik der LVA Baden (Heidelberg, Germany), among others, enrolled 80 chemotherapy-naïve patients with locally or advanced metastatic nsclc (Stage IIIb=36%, Stage IV=64%). Patients were randomized into 2 arms; in arm A, patients were treated with pemetrexed (500 mg/m^2) IV infusion and IV carboplatin (AUC 6) (n=39), and in arm B (n=41) with IV oxaliplatin (120 mg/m^2), both in 21-day cycles, supplemented with vitamins and dexamethasone.

Response rates for the two regimens were similar and toxicity was low compared to other platinum combinations. Confirmed response rate was 33% in arm A, and disease stabilized in 41% of patients, whereas in arm B, confirmed response rate was 27% and disease stabilized in 44%. Observed Grade 3/4 hematologic toxicities in arm A included neutropenia (27%), febrile neutropenia (3%), thrombocytopenia (18%), and anemia (8%). In arm B there were no Grade 4 hematologic toxicities, but Grade 3 neutropenia (5%), thrombocytopenia (2%), and anemia (2%) were noted. Furthermore, main nonhematologic toxicities in arm A included Grade 3 fatigue (8%) and stomatitis (3%), while Grade 3 vomiting (7%), neuropathy (2%), diarrhea (2%), and hypersensitivity reactions (2%) were recorded in arm B (Scagliotti G, etal, ASCO03, Abs. 2513).

A multicenter, nonrandomized, phase II clinical trial (protocol #5142) sponsored by Eli Lilly, of pemetrexed plus oxaliplatin for first-line treatment of advanced colorectal cancer, was initiated in May 2002, at the University of Pittsburg Cancer Center and Allegheny Cancer Center (Pittsburgh, PA), among others, to determine the anticancer effects of pemetrexed in combination with oxaliplatin. According to the protocol, patients were administered pemetrexed (500 mg/m^2) and oxaliplatin (120 mg/m^2) in 21 day cycles, for 6 cycles or until progression. Among 54 treated patients, 23% developed Grade 3/ 4 neutropenia, and 2 experienced neutropenic fever. Grade 4 thrombocytopenia was observed in 1 patient. Various grades of neurosensory toxicity were noted (Grade 0=17%, Grade 1=68%, Grade 2=11%, Grade 3=4%, Grade 4=0%); there were no cases of Grade 4 diarrhea. Nonhematologic toxicities included an allergic reaction (n=1), stomatitis (n=1), and pulmonary embolism (n=1). While 2 patients died during the trial, their death was probably disease-related, but correlation to the treatment can not be entirely excluded. The regimen was well tolerated and among 47 patients with confirmed responses, there was 1 CR and 10 PR (Atkins JN, et al, ASCO03, Abs. 1103).

A phase I/II clinical trial (protocol #2927) of pemetrexed plus irinotecan administered every 21 days to patients with previously treated, locally advanced or metastatic col-

orectal cancer, sponsored by Eli Lilly, was initiated in April 2002, to determine MTD, toxicity, and effectiveness of pemetrexed and irinotecan as second line treatment for locally advanced or metastatic colorectal cancer. The study, conducted at Gemeinschaftspraxis fur Haematologie und Onkologie (Magdeburg, Germany), New York University School of Medicine (New York, NY), Martin Luther University (Halle-Wittenberg, Germany), among others, enrolled patients with adequate bone marrow, liver and kidney function, previously treated with 5-FU. As a modification to an earlier phase I/II study of pemetrexed and irinotecan, the effects of folic acid and vitamin B12 supplementation were considered in recommending a new MTD.

Patients were administered pemetrexed (500 mg/m^2) in combination with irinotecan at 250 mg/m^2 (group 1, n=3), 300 mg/m^2 (group 2, n=3) or 350 mg/m^2 (group 3, n=6), for 1-9 cycles of therapy. DLT were defined as Grade 4 neutropenia with more than 5 days of fever/infection, Grade 4 thrombocytopenia, any nonhematologic toxicity >Grade 2 (excluding elevated AST/ALT or alkaline phosphatase, or nausea/vomiting in patients not treated with preventive care), or a treatment delay of >2 weeks because of unresolved Grade 3/4 toxicities. There were no Grade 3/4 toxicities in groups 1 and 2 but 3 patients from group 3 experienced DLT manifested as Grade 4 neutropenia with fever and septicemia (n=1), Grade 4 neutropenia for more than 5 days with Grade 3 fatigue (n=1), and Grade 3 fatigue (n=1). MTD was established at 500/350 (pemetrexed/irinotecan). There was 1 PR (group 3), and disease stabilized in 7 patients (group 1=1; group 2=3 group 3=3), and progressed in 4 (group 1=2, group 3=2) (Kroening H, et al, ASCO03, Abs. 1459).

Pemetrexed is currently primarily evaluated in combination regimens with established cytotoxic agents with different mechanisms of action. However, it may also have a role in combinations with regulatory/cytostatic agents. Pemetrexed's target, thymidylate synthase (TS), is an essential enzyme for the *de novo* synthesis of thymine nucleotides required in DNA synthesis and, therefore, an important target for antitumor therapies. Effectiveness of agents targeting TS is inversely related to TS expression. Additionally, chronic exposure of cells to anti-TS inhibitory agents can cause resistance from increased TS expression. Use of an antisense oligodeoxynucleotide targeting TS has been shown to partially reverse TS expression in unselected and 5-FU resistant Hela cells, and enhance sensitivity to 5-FU (Ferguson PJ, etal, Br J Pharmacol, Dec 2001;134(7):1437-46).

The anti-TS oligo ISIS 13783 was investigated in the pemetrexed-resistant GC3mta cell line, a subline derived from GC3 colon carcinoma cells as a result of chronic exposure to the drug. Expression of TS mRNA and protein are respectively 30-fold and 40-fold higher in GC3mta cells. Both cell lines were exposed for ISIS 13783 or a control scrambled sequence (ISIS 129691) in the presence of cationic lipids. Exposure to the anti-TS oligo caused a reduction in the TS/beta-actin mRNA ratio by 70% in both the GC3mta and GC3 cells, with a corresponding decrease in TS protein in GC3mta cells (TS protein levels in GC3 cells were too low to make a meaningful comparison). When sensitivity of these cells to pemetrexed was tested in an antiproliferative assay after transfection with ISIS 13783, transfection of oligos directed against TS greatly enhanced the sensitivity of GC3 parental colon carcinoma cells to pemetrexed, and partially restored the sensitivity of GC3mta cells to the drug (Chen VJ, AACR03, Abs. R605).

Provenge

Provenge (APC8015), under development by Dendreon, is a cellular vaccine consisting of autologous peripheral blood mononuclear cells (PBMC) enriched for a dendritic cell fraction, which is pulsed with a prostatic acid phosphatase (PAP)-granulocyte macrophage colony stimulating factor (GM-CSF) construct.

In September 2001, enrollment was completed in the phase III double blind, placebo-controlled, phase III clinical trial (protocol ID: D9901), which commenced in January 2000. Approximately 240 men suffering from advanced prostate cancer were to be recruited for the trial, which involves 30 clinical sites nationwide. To be eligible for the trials, patients must have metastatic prostate cancer that has progressed following hormone therapy. Patients must also be free of cancer-related pain. Patients are being treated with a total of 3 immunotherapy treatments over 30 days. Each treatment consists of an apheresis procedure to collect blood cells, followed 2 days later by an infusion of dendritic cells containing vaccine. Patients who are administered the placebo will have the option of being treated with the immunotherapy if their disease progresses during the study.

Dendreon is conducting 3 ongoing phase III clinical trials, with Provenge, two trials for the treatment of HRPC, as well as an additional trial in men with hormone-sensitive prostate cancer, an earlier stage of disease. In January 2002, an interim analysis of the first phase III clinical trial (protocol ID: D9902) of Provenge therapeutic vaccine in advanced prostate cancer, provided by an independent, third party, was inconclusive and did not provide a sufficient basis upon which to make definitive business decisions relating to the ongoing development of Provenge. It indicated that it was possible, but not probable, that the primary endpoint of the study wound be achieved. The interim analysis addressed data in the first of two identical clinical trials of Provenge in HRPC, and did not address a secondary endpoint of delay in the onset of disease-related pain. Dendreon noted that, as it prepares to seek marketing approval for Provenge, additional trials may be required to supplement the ongoing phase III development program.

In the multicenter, randomized, placebo-controlled, phase III clinical trial (protocol ID: 9901), conducted by UCSF, University of Washington (Seattle, WA), Sharp

Healthcare (San Diego, CA), US Oncology and Eastern Virginia Medical School (Norfolk, VA), among others, 127 patients with asymptomatic metastatic androgen-independent prostate cancer were randomized in a 2:1 ratio to either Provenge (n = 82) or placebo (n = 45), every two weeks, for 3 cycles. To be eligible patients must have >25% of cancer cells positive for prostatic acid phosphatase (PAP) by central pathology review. The primary endpoint was TTP on bone scan or CT scan, while secondary endpoints included onset of disease-related pain. Disease progressed in 114/127 patients at the time of data analysis. Overall, there was a trend toward improved TTP in the Provenge arm (HR=1.39). Longer TTP was associated with lower Gleason score.

A subset analysis revealed that in patients with Gleason score of ≤7, TTP was 9.0 weeks in the placebo group and 16.0 weeks in the Provenge group for an HR of 2.2. There was also a higher probability that patients with Gleason score ≤7, treated with Provenge, would remain free of cancer-related pain. Provenge therapy was well tolerated. In summary, although a statistically significant improved median TTP was not observed with Provenge, the trend toward improvement and the subset analysis, along with the drug's minimal toxicity profile, warrant further investigation. A confirmatory phase III clinical trial in patients with Gleason score ≤7 is in progress (Small E J, etal, ASCO03, Abs. 1534).

Provenge treatment also induced a highly significant T-cell mediated immune response compared to placebo, with Provenge-treated patients demonstrating an eight-fold increase in T-cell proliferation compared to placebo. In addition, among men treated with Provenge, those whose tumors graded with a Gleason score ≤7 developed a median change in T-cell mediated immune response seven-fold greater than that seen in Provenge-treated men whose tumors were graded a Gleason score ≥8.

Patients treated with Provenge whose disease had not progressed six months after randomization, had a greater than eight-fold advantage in PFS compared to those patients who were treated with placebo (34.7% versus 4%). Overall, Provenge was well tolerated, with the most common side effects being chills and fever, which were most often infusion-related (Schellhammer P, etal, ASCO02, Abs. 731:183a).

In December 2002, Dr. Paul Schellhammer, professor and chief of urology at Eastern Virginia Medical School, presented results at the 2002 meeting of the Society of Urologic Oncology in Bethesda, MD, indicating that, in addition to delaying TTP, the vaccine delayed onset of disease-related pain in patients with hormone-resistant (androgen-independent) prostate cancer with a Gleason score of ≤7. Delay in the onset of cancer-related pain was the secondary endpoint of study D9901, which enrolled only patients who did not have cancer-related pain at the time of entry. In patients with a Gleason score of ≤7, those treated with Provenge remained pain free significantly longer than those on placebo. For Provenge-treated patients, the probability of remaining free of cancer-related pain while on the study was over 2.5-fold higher than for patients treated with placebo, indicating an HR of 2.6%. As with the previously reported TTP data in study D9901, no apparent benefit on the pain endpoint was observed among patients with Gleason scores of ≥8.

In October 2002, Dendreon resumed patient enrollment in the second phase III clinical trial (protocol ID: D9902) of Provenge in HRPC. Dendreon had suspended enrollment of new patients into the D9902 trial, following a request from the FDA in late April 2002, pending submission of additional information on the manufacture and characterization of Provenge. In December 2002, the protocol for the placebo-controlled, multicenter (n=15), phase III clinical trial (protocol ID: D9902) of Provenge vaccine in men with HRPC was amended following discussions with the FDA. Investigators will enroll only patients with a Gleason score of ≤7; patients must have rising PSA and no cancer-related pain. The trial will measure TTP and development of cancer-related pain.

In June 2003, Dendreon received a Special Protocol Assessment (SPA) from the FDA indicating that its pivotal phase III clinical trial (protocol ID: D9902B) will serve as the basis for a Biologics License Application (BLA) for the Provenge cancer vaccine for the treatment of androgen-independent prostate cancer. The SPA is a binding written agreement that provides for sponsors to receive official FDA evaluation on pivotal trials that will form the basis of final approval. Through this process, Dendreon worked closely with the FDA to ensure that the trial's design and planned analysis adequately addresses the clinical, statistical and regulatory objectives.

D9902B, a randomized double-blind, placebo-controlled, phase III trial of Provenge is underway and will enroll approximately 275 patients at more than 60 medical centers throughout the USA. To be eligible for the study, patients must have metastatic prostate cancer that has progressed following hormone therapy and have a Gleason score of ≤ 7. Patients must also be free of cancer-related pain. According to the protocol, patients are treated with a total of 3 immunotherapy treatments over 30 days. Each treatment consists of an apheresis procedure to collect blood cells, followed two days later by an infusion of dendritic cells containing vaccine. Patients treated with placebo will have the option of being treated with the immunotherapy regimen if their disease progresses during the trial.

PSA-based Vaccine

Therion Biologics is developing several immunization approaches for the treatment of cancer. Prostvac VF, is an immunization approach that combines a recombinant vaccinia virus (rV) that expresses the PSA gene (rV-PSA), and a recombinant fowlpox virus containing the PSA gene (rF-PSA), with an rV that expresses B7.1 costimulatory gene

(rV-B7.1). This construct is being evaluated in a randomized phase II clinical trial (protocol IDs: NCI-02-C-0218, NCI-5319), in combination with docetaxel, in metastatic androgen-independent prostate cancer. The trial is being conducted by the NCI with Philip M. Arlen, MD, as Protocol Chair.

Although weekly docetaxel has been shown to have activity against androgen-independent prostate cancer, most patients who initially respond to this therapy eventually die from the disease. Preclinical studies have shown that taxane-based chemotherapy can enhance antitumor response of vaccines in mice, which appears to be schedule dependent. This trial was designed to determine if the vaccine could be administered in combination with docetaxel without added toxicity, and if concurrent docetaxel has any effect on the patient's ability to mount an immune response to the vaccine.

According to the protocol, patients are treated with SC GM-CSF (100 μg) for 4 days with each vaccination. In the priming portion of the trial, all patients are administered recombinant vaccinia-prostate-specific antigen (PSA) vaccine SC and recombinant rV-B7.1 vaccine SC on day 1, and sargramostim (GM-CSF) SC (100 μg) on days 1-4. Patients are then treated with fowlpox-PSA vaccine (F-PSA) SC on day 15 and GM-CSF SC on days 15-18. In arm A, patients are premedicated with dexamethasone and treated with IV docetaxel (30 mg/m^2), over 30 minutes, weekly on days 29, 36, and 43; F-PSA SC on day 30; and GM-CSF SC on days 30-33. Treatment repeats beginning on day 56 for one more course. Patients whose disease has not progressed at day 85 are treated with docetaxel weekly for 3 weeks and F-PSA on day 1 of each course. In arm B, patients are treated with F-PSA SC on days 29 and 57 and GM-CSF SC on days 29-32 and 57-60. Patients whose disease progresses after day 85, either radiographically or by rising PSA, stop being treated with the vaccine but may be treated with docetaxel weekly for 3 weeks. Chemotherapy repeats every 4 weeks in the absence of disease progression or unacceptable toxicity.

Among 10 patients randomized to either arm A (n=5) or arm B (n=5), median on study PSA was 120 ng/ml (range=16-534). Median time on the trial in arm A is 102 days (5-146+ days), and 55 days (5-138+ days) in arm B. In arm A, 4/5 patients remain on trial (1 patient died from disease progression), and 3/5 patients in arm B. Grade 3 toxicities consisted of 1 skin reaction attributable to vaccinia that resolved spontaneously, and hyperglycemia following dexamethasone. Based on ELISPOT assay testing, after 3 vaccinations, increases in T-cell precursor frequency as great as 4-fold were detected in both arms. Thus, it appears that dexamethasone premedication and weekly docetaxel do not blunt specific T-cell responses generated by the PSA vaccine. If continued robust immunologic responses are seen with the combination, this trial will be followed with a larger one using clinical endpoints (Arlen PM, etal, ASCO03, Abs. 1701).

Rubitecan

Rubitecan (Orathecin; SuperGen) is a third-generation, water-insoluble camptothecin analog, targeting topoisomerase I. Rubitecan has completed a phase III clinical trial in refractory pancreatic cancer and, in December 2002, SuperGen (Dublin, CA) began a 'rolling' submission of an NDA for rubitecan for refractory (resistant) pancreatic cancer. The first module submitted contained the chemistry, manufacturing and controls (CMC) section. In February 2003, SuperGen submitted to the FDA the second of three data modules of this NDA, which contained the preclinical information on rubitecan. The NDA submission will contain data on over 2,700 patients treated with rubitecan in more, than 43 clinical trials and will be based on the company's phase III clinical program, the largest randomized pancreatic cancer trial program ever initiated worldwide. The submission will also be supported by data from a phase II clinical trial of rubitecan in refractory pancreatic cancer, presented at ASCO00 and reviewed by an independent third-party expert radiology review panel. SuperGen is actively finalizing the third and last section of its NDA.

In November 2002, the FDA designated oral rubitecan as a 'fast track' product for the treatment of patients with locally advanced or metastatic pancreatic cancer that is resistant or refractory to standard chemotherapy. In June 2003, SuperGen's European affiliate, EuroGen Pharmaceuticals, was granted orphan medical product designation by the EMEA for Orathecin as a treatment of pancreatic cancer.

In May 2003, during a satellite symposium held in Chicago before the 2003 meeting of the American Society of Clinical Oncology (ASCO03), Howard Burris, MD, Director of Drug Development at the Sarah Cannon Cancer Center (Nashville, TN), presented results from a phase III clinical trial of rubitecan as third-line treatment for refractory or resistant pancreatic cancer. The trial randomized 409 patients, most of whom had previously failed two or more chemotherapies, to rubitecan or 'best choice'. Approximately 90% of patients in the 'best choice' group were treated with a chemotherapeutic agent such as gemcitabine, 5-FU, mitomycin C, capecitabine, or docetaxel. The primary trial endpoint was overall survival with secondary endpoints of tumor response and TTP.

Among 196 patients randomized to rubitecan, there were 13 (7%) responses (CR+PR), compared to 1 (<1%) among 211 patients treated with other 'best choice' chemotherapeutics. This finding is statistically significant and independently verified. Among these 13 responders, MST was 336 days, and median TTP was 246 days. In addition, disease stabilized in 40/196 (20%) of patients randomized to rubitecan compared to 17/211 (8%) for those in 'best choice' regimens. This finding is also statistically significant and independently verified. The total number of patients achieving 'disease control', defined as CR plus PR plus stable disease, was 53/196 (27%) with rubitecan, com-

pared to 18/211 (9%), for 'best choice' treatment. Median TTP was 57 days for patients on rubitecan, versus 47 days for those on 'best choice' regimens. This finding is also statistically significant. MST of patients on Orathecin was 108 days versus 93 days in those treated with 'best choice', but the difference was not statistically significant. Results were confounded by the fact that approximately half of the patients randomized to the 'best choice' treatment were treated with Orathecin when they failed 'best choice'. As a result of this 'rescue therapy', 302/409 (74%) patients were treated with rubitecan.

Toxicities were generally manageable with fewer than 5% of patients in either arm needing to discontinue therapy for drug-related toxicity. Severe or most frequent adverse events with an incidence >5% in patients treated with rubitecan, compared to 'best choice' included asthenia (20% versus 18%), abdominal pain (17% versus 12%), pain (5% versus 6%), sepsis (5% versus 7%), deep thrombophlebitis (5% versus 5%), nausea (14% versus 9%), anorexia (6% versus 10%), diarrhea (9% versus 5%), vomiting (12% versus 8%), leucopenia (22% versus 13%), anemia (16% versus 9%), thrombocytopenia (9% versus 10%), dehydration (15% versus 12%), bilirubinemia (7% versus 2%) and dyspnea (8% versus. 6%), respectively.

Satraplatin

Satraplatin (JM-216), a novel oral platinum (IV) analog, was originally developed by Johnson Matthey (London, UK) and licensed to Bristol-Myers Squibb. In January 2002, the IND for satraplatin was transferred from Bristol-Myers Squibb to NeoOncoRx, now Spectrum Pharmaceuticals (Irvine, CA). Subsequently, in October 2002, Spectrum licensed the worldwide rights to satraplatin to GPC Biotech (Martinsried, Germany and Waltham, MA). In September 2003, GPC Biotech received written confirmation from the FDA to initiate a phase III registrational clinical trial with satraplatin plus prednisone in patients with HPRC who have failed prior treatment with chemotherapy. This notification is the culmination of a satisfactory completion of both a Special Protocol Assessment (SPA) and an "end of phase II" meeting with the FDA. The satraplatin registrational phase III clinical trial will assess the safety and efficacy of satraplatin in combination with prednisone as a second-line chemotherapy regimen in patients with HRPC. The primary endpoint of this multinational, randomized, phase III clinical trial, to enroll an estimated 800 patients, is TTP. Other objectives include the evaluation of pain control and survival as well as an assessment of the drug's safety in this patient population. With an estimated 100,000 patients in North America, Europe and Japan diagnosed with HRPC annually, the company estimates the market opportunity for this indication alone at $150 million.

Satraplatin has shown activity against HRPC in cisplatin-resistant human tumor lines, and in phase I clinical trials. A multinational, randomized, phase III clinical trial (protocol ID: BMS-CA142-025; EORTC-30972), to compare satraplatin plus prednisone to prednisone alone patients with refractory HRPC, was closed in 1999 after only 50 patients out of the 380 planned, had been enrolled. Bristol-Myers Squibb, at the time the developer of satraplatin under a worldwide license, closed the trial because the company had decided to discontinue development of the drug. Primary trial objectives were to compare the treatment arms in terms of survival and time-to-pain progression. Progression was defined as a ≥1 point increase in pain score or the need of radiotherapy for pain, ≥2 point worsening in pain score, progression of measurable or nonmeasurable disease, or confirmed doubling of PSA over baseline level to >20 ng/ml.

Patients were treated with either satraplatin (100 mg/m^2) for 5 days, plus PO prednisone (10 mg) *bid*, or prednisone alone. All 50 patients finished treatment and were followed up until progression or death. To date, 48 of 50 have progressed and 42 have died, most from prostate cancer. A >50% decrease in PSA was seen in 2/23 (8.7%) patients on the prednisone alone arm, and in 9/27 (33.3%) in the satraplatin plus prednisone arm. Toxicity was minimal in both arms; 1 patient on each arm died from stomach perforation, most likely related to prednisone. Compliance to treatment was excellent. Overall survival was 11.86 months in the prednisone arm (n=23), compared to 14.88 months in the combination arm (n=27). PFS was 2.53 months in the prednisone arm, and 5.16 months in the combination arm. Although analysis lacks power because only 50 patients were entered, this combination shows promise in HRPC and will be further evaluated (Sternberg CN, etal, ASC003, Abs.1586).

Thalidomide

Thalidomide, an antiangiogenic compound, was commercialized by Celgene for the treatment of erythema nodosum leprosum (ENL) in October 1998, after obtaining FDA approval in July 1998. Since then this agent has been used extensively off-label, primarily in the treatment of multiple myeloma, and in being investigated in clinical trials, alone or in combination with various chemotherapy regimens, in numerous clinical trials.

A randomized phase II clinical trial of weekly docetaxel alone or in combination with thalidomide was carried out at Mehr Medical Center (Tehran, Iran) in metastatic HRPC. Accrual began in October 2001. Among 55 chemotherapy-naïve patients accrued for the trial, 30 were randomized to arm A and 25 to arm B. In arm A, IV docetaxel (35 mg/m^2) was administered weekl, for 6 consecutive weeks, followed by 2 weeks rest, plus PO thalidomide (100 mg) every day. In arm B, patients were treated with weekly docetaxel alone at the same dose and schedule. All patients in both arms were administered daily prophylactic anticoagulation treatment throughout the study to prevent thrombotic episodes.

A total of 660 weekly docetaxel infusions were administered. Neutropenia ≥Grade 2 was seen only in 5 patients and ≥Grade 2 patients thrombocytopenia in 3 patients.

DVT developed in 2 in arm A, which cleared shortly after the initiation of anticoagulant. Based on generally accepted consensus criteria, 20/30 (66%) patients in the combination arm experienced a PSA decline of ≥50% compared with 8/25 (32%) patients on docetaxel monotherapy. Results from this trial support previous preclinical and clinical evidence suggesting that there is a synergistic effect of combining an antiangiogenic agent with a cytotoxic drug in the treatment of prostate cancer (Salimichokami M, ASCO03, Abs. 1725).

In April 2000, a randomized, double-blind, crossover, placebo-controlled, phase III clinical trial (protocol ID: NCI-00-C-0080, NCI-T99-0053) of PO thalidomide in patients with androgen-dependent nonmetastatic prostate cancer after limited hormonal ablation, was initiated to determine TTP, toxicity, pharmacodynamics, and assess changes in molecular markers of angiogenesis.

Tirapazamine

Tirapazamine (Tirazone; Sanofi-Synthelabo) is a benzotriazene cytotoxic that is bioreduced under hypoxic conditions to an active free radical species, which cause single and double strand DNA breaks.

A randomized phase II clinical trial (protocol ID: TROG 98.02) was conducted in Australia by the Trans-Tasman Radiation Oncology Group (TROG), to select a chemoradiotherapy regimen as the experimental arm for an currently ongoing phase III clinical trial in advanced squamous cell carcinoma of the head and neck (SCCHN). Tirapazamine produced promising results in a phase I clinical trial, in combination with radiotherapy and cisplatin.

In the phase II clinical trial, 122 previously untreated patients (neither chemotherapy nor radiotherapy) from 13 institutions with Stage III or IV SCCHN of the oral cavity, oropharynx, hypopharynx or larynx, were enrolled between September 1998 and May 2002, and randomized 1:1 to either arm A to be treated with cisplatin (50 mg/m^2) on day 1 and infusional 5-FU (360 mg/m^2/day) on days 1-5, of weeks 6 and 7, or arm B to be treated with cisplatin (75 mg/m^2) plus tirapazamine (290 mg/m^2/day) on day 2 of weeks 1, 4 and 7 and tirapazamine alone (160 mg/m^2/day) on days 1, 3 and 5 of weeks 2 and 3. Radiotherapy for all patients was 70Gy delivered in 7 weeks.

Among the first 63 patients to enroll, 79% had Stage IV SCCHN with T4 and/or N3, 47% in arm A and 57% in arm B. One-year PFS was 58% in arm A and 76% in arm B. One-year locoregional control was 61% and 79%, and one-year overall survival was 77% and 90%, respectively. Chemotherapy-related toxicity was more common in arm B, including Grade 3 and 4 neutropenia, emesis, cramps and fatigue. The only significant difference in radiation toxicities was a more prolonged acute skin reaction in patients in arm A.

In terms of radiation therapy, 96% in arm A and 91% in arm B were treated with >95% planned radiation dose to all treated sites. Week 7 chemotherapy was omitted in 50% in arm B, but compliance with chemotherapy in weeks 1-4 was good with 91 % treated with >2 cisplatin doses and >7 tirapazamine doses.

This interim analysis of the first 63 patients was conducted after the protocol was amended from its initial accrual target of 60 to 120 patients. The study was expanded in order to more reliably assess the feasibility and safety of the regimens in the multicenter setting. The primary efficacy endpoint, with this amendment, was failure-free survival (Rischin D, etal, ASCO03, Abs. 1992).

Among 121 evaluable patients (1 patient was ineligible) 79% were Stage IV in arm A, compared to 83% in arm B, and 67% had cancer of the oropharynx in arm A, compared to 73% in arm B. Exposure to radiotherapy was similar in the two treatment arms. Radiotherapy at >66 Gy was delivered in 88% of patients in arm A and 87% in arm B. Radiotherapy was delivered for >56 days in 93% of patients in Arm A and 92% of patients in arm B. Although chemotherapy regimen compliance was good in the first 4 weeks, the third dose during week 7 in arm B was frequently (~50%) omitted.

Toxicities are summarized below. After a median follow-up of 2.6 years (range=0.4-4 years), there was 1 death in arm A and 2 in arm B, all from pneumonia. There were no febrile neutropenia-related deaths.

	Arm A (cisplatin + 5-FU + RT) incidence (%)			Arm B (cisplatin + tirapazamine + RT) incidence (%)		
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis	28	72	0	13	80	5
RT dermatitis	44	58	0	51	18	0
Neutropenia		13	4		30	7
Febrile neutropenia		6	0		15	0
Thrombocytopenia	2	4	0	2	3	2
Nausea	28	4	0	29	13	0
Vomiting	15	2	0	26	5	0
Diarrhea	6	2	0	16	6	0
Cramping	0	0	0	53	13	2
Skin rash	0	0	0	11	5	0
Fatigue	24	13	0	53	5	0

In terms of response, based on tumor oxygenation status, treatment failed locoregionally in 1/10 (10%) of nonhypoxic tumors in arm A, and in 2/3 (67%) in arm B, compared to 8/13 (61.5) for hypoxic tumors in arm A and 1/19 (5.3%) in arm B. Relative HR in hypoxic tumors was 2.95 in arm A and 0.18 in arm B. In terms of failure-free survival, treatment failed in 3/10 (30%) patients with nonhypoxic tumors in arm A and in 2/3 (67%) in arm B, compared to 11/13 (84.6%) with hypoxic tumors in arm A and 5/19 (26.3%) in arm B. Relative HR was 2.34 in arm A and 0.51 in arm B. There were 7/10 (70%) CR in nonhypoxic tumors in arm A compared to 3/3 (100%) in arm B, and 4/13 (31%) in hypoxic tumors in arm A and 14/19 (74%) in arm B.

Based on the results of this trial, a large phase III clinical trial (HeadStart) has been initiated to evaluate cisplatin and radiotherapy with cisplatin plus tirapazamine and radiotherapy in advanced SCCHN.

A phase III clinical trial (protocol ID: S0003), conducted by the Southwest Oncology Group (SWOG), evaluated paclitaxel plus carboplatin with or without tirapazamine in advanced nsclc. This trial was designed to determine if a paclitaxel/cisplatin/tirapazamine combination offered a survival advantage over paclitaxel plus cisplatin, and to dose escalate tirapazamine on cycle 2 to achieve maximal cumulative dosing. The trial's primary endpoint was determination of overall survival and PFS. The trial was powered to demonstrate a 37% improved survival over control (11 months versus 8 months). Secondary endpoints included response rate and toxicity.

The impact of tirapazamine on survival has varied in past combination trials. In the CATAPULT I clinical trial in Stage IIIb or IV nsclc, an improvement in survival (MST=34.6 weeks versus 27.7 weeks; 1-year survival=33% versus 22%) was seen with the combination of tirapazamine (390 mg/m^2) and cisplatin (75 mg/m^2) compared with cisplatin alone, when administered on day 1 of a 21-day cycle. However, in CATAPULT II the combination of tirapazamine (390 mg/m^2) and cisplatin showed no survival advantage when compared to etoposide (100 mg/m^2) and cisplatin. A high early dropout rate was also a problem in the tirapazamine (390 mg/m^2) and cisplatin arm attributable to toxicity.

In this phase III clinical trial, 396 chemotherapy-naïve patients were enrolled between November 2000 and November 2002, with 377 being eligible. Patients were randomized in arm A (n=187) to treatment with paclitaxel (225 mg/m^2) infused over 3 hours in combination with cisplatin (AUC=6), or in arm B (n=190) to treatment with paclitaxel and cisplatin as in arm A, and tirapazamine (260 mg/m^2) in cycle 1, escalated to 330 mg/m^2 in cycle 2 if there was no unacceptable toxicity, administered on day 1, every 21 days.

The trial was closed early after an interim analysis made it clear that the goal of this combination regimen of a 37.5% improvement in survival was untenable. There were a number of problems with this trial, including incidence of significant toxicity. Patients on the tirapazamine arm experienced significantly more abdominal cramps, fatigue, transient hearing loss, febrile neutropenia, hypotension, myalgias, skin rash, and were removed from treatment more often because of toxicity (25% versus 10%). Also 44% of patients were not administered the higher tirapazamine dose, primarily because of toxicity. Among 183 evaluable patients in arm B, response rates were 1% CR and 23% PR, compared to 2% CR and 32% PR in arm A. MST was 8 months and PFS 5 months in arm B, compared to 9 months and 4 months in arm A. Therefore, adding tirapazamine to the paclitaxel/cisplatin regimen does not result in improved survival but increases toxicity (Williamson S K, etal, ASCO03, Abs. 2502).

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FUTURE ONCOLOGY

PUBLISHED BY **NEW MEDICINE, INC.**

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SUBSCRIPTION INFORMATION:

- FUTURE ONCOLOGY (ISSN 1082-331X) is published as 12 issues (several double issues) per subscription period, with a free index listing companies/institutions and subjects covered.
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