Drugs Fut 2006, 31(7): 625-639

CCC: 0377-8282/2006

Update 2006 - Treatment of Head and Neck Cancer

(Source: Prous Science Integrity®)

Treatment of Head and Neck Cancer by Condition

Condition	Phase	Drug	Source
Head and neck cancer	L-2006	Cetuximab[1,2]	Merck KGaA
	III	Advexin®	Introgen/NCI
	III	Bleomycin sulfate[1]	Inovio Biomedical
	III	Carboplatin[1,2]	NCI
	III	Gefitinib[1,2]	AstraZeneca/NCI
	III	Tirapazamine[2]	Sanofi-aventis
	II	ABI-007	Abraxis BioScience
	II	AP-5346[2]	Access Pharmaceuticals
	II	Erlotinib hydrochloride[1,2]	OSI Pharmaceuticals/Genentech
	II	Gemcitabine[1,2]	NCI
	II	Imatinib mesilate[1,2]	Institut Gustave Roussy
	II	Irinotecan hydrochloride[1,2]	NCI
	II	IRX-2	IRX Therapeutics
	II	Ispinesib mesilate	NCI
	II	Lapatinib[2]	GlaxoSmithKline/NCI
	II	Multikine®	Cel-Sci
	II	OncoVEX^{GM-CSF}	BioVex
	II	Paclitaxel[1,2]	Bristol-Myers Squibb/NCI
	II	Perifosine[2]	NCI
	II	Sorafenib[1,2]	NCI
	II	VB4-845	Viventia Biotech
	I/II	ABT-510[2]	M.D. Anderson Cancer Center
	I/II	Bevacizumab[2]	NCI
	I/II	Combretastatin A-4 phosphate	OxiGene
	I/II	Zalutumumab	Genmab/Medarex
	I	ARQ-501	ArQule/Roche
	I	AZD-2171	AstraZeneca
	I	EM-1421	Duke University/Erimos/University of South Carolina
	I	Fenretinide[2]	NCI
	I	Lonafarnib[2]	NCI
	I	Lontucirev (replicating adenovirus)	NCI
	I	Lovaxin C	Advaxis
	I	Motexafin gadolinium	Pharmacyclics
	I	p53-DC Vaccine	University of Pittsburgh
Mouth cancer	III	Celecoxib[1,2]	NCI
	II	Advexin®	NCI
	II	Erlotinib hydrochloride[2]	NCI
	II	Multikine®	Cel-Sci
Nasopharyngeal cancer	I	Valproic acid	Johns Hopkins University
Pharyngeal cancer	II	Advexin®	NCI
Rhinopharyngeal cancer	R-2005	H-101	Shanghai Sunway Biotech
	II	Bortezomib[1]	NCI
	II	Capecitabine[1,2]	NCI
	II	Gemcitabine[1,2]	NCI
	II	Nimotuzumab[2]	YM BioSciences
Salivary gland cancer	III	Celecoxib[1,2]	NCI
	II	Carboplatin[1,2]	National Cancer Institute of Canada
	II	Gemcitabine[1,2]	National Cancer Institute of Canada/NCI/Dana-Farber Cancer Institute

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Treatment of Head and Neck Cancer by Source

Source	Condition	Drug	Phase
Abraxis BioScience	Head and neck cancer	ABI-007	II
Access Pharmaceuticals	Head and neck cancer	AP-5346[2]	II
Advaxis	Head and neck cancer	Lovaxin C	I
ArQule	Head and neck cancer	ARQ-501	I
AstraZeneca	Head and neck cancer	AZD-2171	I
		Gefitinib[1,2]	III
BioVex	Head and neck cancer	OncoVEX$^{GM\text{-}CSF}$	II
Bristol-Myers Squibb	Head and neck cancer	Paclitaxel[1,2]	II
Cel-Sci	Head and neck cancer	Multikine®	II
	Mouth cancer	Multikine®	II
Dana-Farber Cancer Institute	Salivary gland cancer	Gemcitabine[1,2]	II
Duke University	Head and neck cancer	EM-1421	I
Erimos	Head and neck cancer	EM-1421	I
Genentech	Head and neck cancer	Erlotinib hydrochloride[1,2]	II
Genmab	Head and neck cancer	Zalutumumab	I/II
GlaxoSmithKline	Head and neck cancer	Lapatinib[2]	II
Inovio Biomedical	Head and neck cancer	Bleomycin sulfate[1]	III
Institut Gustave Roussy	Head and neck cancer	Imatinib mesilate[1,2]	II
Introgen	Head and neck cancer	Advexin®	III
IRX Therapeutics	Head and neck cancer	IRX-2	II
Johns Hopkins University	Nasopharyngeal cancer	Valproic acid	I
M.D. Anderson Cancer Center	Head and neck cancer	ABT-5102	I/II
Medarex	Head and neck cancer	Zalutumumab	I/II
Merck KGaA	Head and neck cancer	Cetuximab[1,2]	L-2006
National Cancer Institute of Canada	Salivary gland cancer	Carboplatin[1,2]	II
		Gemcitabine[1,2]	II
NCI	Head and neck cancer	Advexin®	III
		Bevacizumab[2]	I/II
		Carboplatin[1,2]	III
		Fenretinide[2]	I
		Gefitinib[1,2]	III
		Gemcitabine[1,2]	II
		Irinotecan hydrochloride[1,2]	II
		Ispinesib mesilate	II
		Lapatinib[2]	II
		Lonafarnib[2]	I
		Lontucirev (replicating adenovirus)	I
		Paclitaxel[1,2]	II
		Perifosine[2]	II
		Sorafenib[1,2]	II
	Mouth cancer	Advexin®	II
		Celecoxib[1,2]	III
		Erlotinib hydrochloride[2]	II
	Pharyngeal cancer	Advexin®	II
	Rhinopharyngeal cancer	Bortezomib[1]	II
		Capecitabine[1,2]	II
		Gemcitabine[1,2]	II
	Salivary gland cancer	Celecoxib[1,2]	III
		Gemcitabine[1,2]	II
OSI Pharmaceuticals	Head and neck cancer	Erlotinib hydrochloride[1,2]	II
OxiGene	Head and neck cancer	Combretastatin A-4 phosphate	I/II
Pharmacyclics	Head and neck cancer	Motexafin gadolinium	I
Roche	Head and neck cancer	ARQ-501	I
Sanofi-aventis	Head and neck cancer	Tirapazamine[2]	III
Shanghai Sunway Biotech	Rhinopharyngeal cancer	H-101	R-2005
University of Pittsburgh	Head and neck cancer	p53-DC Vaccine	I
University of South Carolina	Head and neck cancer	EM-1421	I
Viventia Biotech	Head and neck cancer	VB4-845	II
YM BioSciences	Rhinopharyngeal cancer	Nimotuzumab[2]	II

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Drugs Under Development for the Treatment of Head and Neck Cancer

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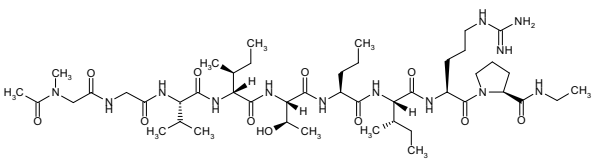
ABI-007

ABI-007 is an injectable suspension comprised of protein-bound paclitaxel nanoparticles that was launched by the former American Pharmaceutical Partners (APP), now Abraxis BioScience following its merger with its parent company American Bioscience, in 2005 in the U.S. as Abraxane™ for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Abraxis BioScience is evaluating the compound in phase II trials for the treatment of arterial restenosis and for the once-weekly treatment of treatment-naïve patients with metastatic melanoma. Additional phase II trials are ongoing at the company for the treatment of head and neck cancer. Abraxis and the National Cancer Institute (NCI) are jointly conducting phase I/II trials for the treatment of non-small cell lung cancer (NSCLC). Early clinical trials are ongoing at Abraxis to evaluate ABI-007 as adjuvant therapy in combination with doxorubicin and cyclophosphamide for the treatment of breast cancer, while the NCI is conducting additional early clinical trials of ABI-007 in combination with conventional paclitaxel (Taxol®) in patients with advanced metastatic melanoma. ABI-007 is the first in a new class of protein-bound particle drugs made possible by Abraxis BioScience's proprietary nanoparticle albumin-bound (nab™) technology. ABI-007, consisting only of albumin-bound paclitaxel nanoparticles, is free of toxic solvents and demonstrated a superior response rate, almost doubling the reconciled target lesion response rate when compared with the solvent-based Taxol® in a prospectively randomized trial in 460 patients with metastatic breast cancer. Because it contains no toxic solvents, ABI-007 enables the administration of 50% more chemotherapy. It requires no premedication to prevent hypersensitivity reactions and can be given over 30 min using standard i.v. tubing.

ABT-510



The angiogenesis inhibitor ABT-510 is in phase II development by Abbott for the treatment of sarcoma, refractory Hodgkin's and non-Hodgkin's lymphoma (NHL) and NSCLC. The M.D. Anderson Cancer Center is conducting early clinical trials for the treatment of head and neck cancer. ABT-510, a synthetic peptide, mimics the antiangiogenic activity of the naturally occurring protein thrombospondin-1 (TSP-1). The peptide blocks the actions of multiple proangiogenic growth factors known to play a role in cancer-related blood vessel growth, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF) and IL-8. In December 2003, ABT-510 was granted orphan drug designation for the treatment of soft tissue sarcoma.

Original monograph – Drugs Fut 2005, 30(11): 1081.

Advexin®

Introgen's Advexin® gene therapy (Ad5CMV-p53, INGN-201) is in phase III development for the treatment of squamous cell carcinoma of the head and neck. The trials are evaluating both Advexin® monotherapy and Advexin® in combination with the standard chemotherapeutic agents cisplatin and 5-fluorouracil (5-FU). The company has completed phase II trials with Advexin® for the treatment of NSCLC and breast cancer. Phase II tri-

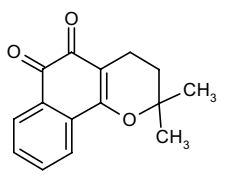
als are also under way at Introgen for the treatment of esophageal cancer, as are phase II trials at the NCI for the combination therapy of cancer of the mouth and throat. Introgen is also evaluating the product in phase I/II trials for the treatment of Li-Fraumeni syndrome. The NCI is evaluating an oral rinse or mouthwash for patients with oral premalignancies in a phase I/II trial pursuant to a Clinical Trials Agreement (CTA) established between Introgen and the Division of Cancer Treatment and Diagnosis (DCTD) of the NCI to co-develop Advexin®. Advexin® has been evaluated in numerous other cancer types and in combination with several standard cancer therapies, including radiation and chemotherapy. Advexin® induces high levels of expression of the tumor suppressor p53 protein in cancer tissue to selectively kill cancer cells. One of the major roles of p53, a normal constituent of cells, is to eliminate cancerous cells by recognizing when the cell has been damaged by mutations and stopping cell growth to initiate repair. If the cell is damaged beyond repair, p53 initiates the cell death pathway to prevent the cell from growing out of control. In 2003, Advexin® was granted orphan drug designation by the FDA for the treatment of head and neck cancer. The product has also received U.S. fast track designation for this indication. Advexin® was developed by Introgen using a gene therapy method licensed exclusively from the University of Texas M.D. Anderson Cancer Center.

AP-5346

AP-5346, a polymer platinate from Access Pharmaceuticals, is in phase II clinical development for the treatment of ovarian and head and neck cancer. Early clinical studies are also under way for solid tumors. The company has filed an IND in the U.S. seeking approval to begin clinical studies with AP-5346 in combination with 5-FU and leucovorin for the treatment of colorectal cancer and preclinical evaluation is under way for its use in melanoma. AP-5346 utilizes Access's proprietary polymer drug delivery system to selectively deliver the cytotoxic DACH platinum to tumors.

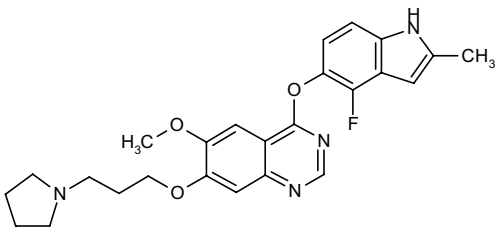
Original monograph – Drugs Fut 2004, 29(6): 561.

ARQ-501



ARQ-501 is an E2F activator in phase II clinical trials at ArQule as monotherapy and/or in combination with other chemotherapy for the treatment of pancreatic cancer and leiomyosarcoma, as well as phase I trials for ovarian and head and neck cancer. ARQ-501, ArQule's most advanced compound developed using its proprietary Activated Checkpoint Therapy^{SM} (ACT^{SM}) platform, activates E2F-mediated checkpoints, leading to selective apoptosis. Based on preclinical data, the company believes that ARQ-501 may offer improved activity and reduced toxicity over conventional chemotherapy and molecular therapy. Originally developed at Beth Israel Deaconess Medical Center and the Dana-Farber Cancer Institute, ARQ-501 was added to ArQule's R&D pipeline following the company's acquisition of Cyclis Pharmaceuticals (formerly CoPharma) in 2003. The compound is being developed under a partnership established between ArQule and Roche in April 2004 focused on the discovery and development of drug candidates targeting the activation of E2F.

AZD-2171



A highly potent inhibitor of VEGF receptor tyrosine kinases developed by AstraZeneca, AZD-2171 is currently undergoing phase II/III trials for the treatment of NSCLC and colorectal cancer. Additional phase II trials are under way at the NCI for the treatment of breast, liver and ovarian cancers, as well as glioblastoma multiforme, melanoma and malignant mesothelioma. Early clinical trials are also under way at AstraZeneca for head and neck cancer and solid tumors and at the NCI for the treatment of acute myeloid leukemia (AML).

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody against VEGF launched in the U.S. in 2004 as Avastin™ by Genentech for the first-line treatment of patients with metastatic colorectal carcinoma in combination with intravenous 5-FU-based chemotherapy. Bevacizumab directly inhibits the biological activity of VEGF and prevents the interaction of VEGF with VEGFR-1 (Flt-1) and VEGFR-2 (KDR), reduces microvascular growth and inhibits the progression of metastatic disease. Bevacizumab also promotes the effective delivery of chemotherapy within the tumor. In January 2005, Roche received EMEA approval for the above indication, and the product is available in several E.U. countries, including Switzerland, Germany and the U.K. Approval has also been obtained in Canada. At present, Roche is seeking

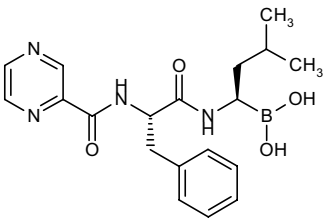
approval for the drug in combination with taxane chemotherapy for locally recurrent or metastatic breast cancer. Chugai has filed a regulatory application in Japan for advanced, recurrent colorectal cancer. Genentech and Roche have filed for regulatory approval for the use of bevacizumab as first-line treatment in combination with paclitaxel and carboplatin for squamous NSCLC. Extensive phase III trials are under way at both Roche and Genentech, including studies for the treatment of renal cell carcinoma, metastatic kidney, ovarian, metastatic pancreatic and prostate cancer. Genentech is conducting phase II trials for the treatment of bladder cancer and in collaboration with the NCI for breast and gastrointestinal cancer. The NCI is also studying the drug for liver cancer and Kaposi's sarcoma, malignant melanoma, malignant mesothelioma, head and neck cancer and solid tumors. The University of Miami is evaluating bevacizumab's potential in macular degeneration. In 2003, Genentech granted Roche rights to bevacizumab outside the U.S., excluding Japan where Roche and Chugai comarket the product. The FDA assigned orphan drug designation to bevacizumab for the treatment of renal cell carcinoma and pancreatic cancer in 2003 and 2004, respectively.

Original monograph – Drugs Fut 2002, 27(7): 625.

Bleomycin Sulfate, New Formulation

Bleomycin sulfate is an antimitotic agent that is marketed by Bristol-Myers Squibb for the treatment of testicular, skin, penile and cervical ancer, vulvar squamous cell carcinoma, Hodgkin's lymphoma and NHL. The drug is currently in phase II/III clinical trials at the NCI for the treatment of Hodgkin's lymphoma in combination with other chemotherapeutic agents with or without radiation therapy, and in phase III trials at Inovio Biomedical for the treatment of head and neck cancer in a novel formulation incorporating Inovio's proprietary MedPulser® technology. MedPulser® is a selective electrochemical tumor ablation system. The system consists of injection of the tumor site with bleomycin, followed by the delivery of an extremely brief, intense, pulsed electrical field via a probe from the MedPulser®, which contains a ring of six electrode needles. Entry of the chemotherapeutic agent into cancer cells is facilitated via aqueous channels in the cell membrane created by the electrical field within the tumor. Although the exact mechanism of action of bleomycin is unknown, available evidence seems to indicate that the main mode of action is inhibition of DNA synthesis, with some evidence of lesser inhibition of RNA and protein synthesis. The drug was originally developed at Bristol-Myers Squibb, and rights to the compound were subsequently licensed to Nippon Kayaku and Inovio (formerly Genetronics).

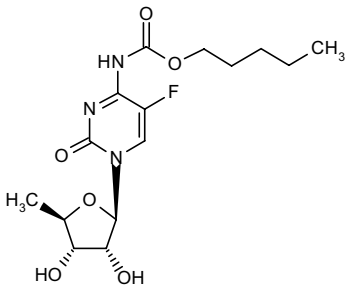
Bortezomib



Bortezomib (Velcade®), a potent and selective proteasome inhibitor, was launched in the U.S. in 2003 by Millennium for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. Inhibition of the proteasome by bortezomib prevents the degradation of intracellular proteins, affecting multiple signaling cascades within cells and leading to cell death and tumor growth inhibition. At present, Millennium is undertaking an extensive clinical development program with the drug, including phase II trials for the treatment of breast, lung and prostate cancers, mantle cell lymphoma and Waldenström's macroglobulinemia. A phase I/II trial for the treatment of amyloidosis is also under way. Phase II trials are ongoing at the NCI for several indications: the treatment of esophageal, gallbladder, kidney, liver and stomach cancers, as well as glioma, leukemia, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), Hodgkin's lymphoma and NHL, myelodysplasia and rhinopharyngeal cancer. Millennium, in collaboration with Johnson & Johnson, is conducting phase II trials for both NSCLC and metastatic NSCLC and phase III trials for the treatment of B-cell lymphoma. Early clinical studies are also under way for anaplastic astrocytoma, colorectal cancer and oligodendroglioma. Millennium is also studying bortezomib for its potential for the treatment of stroke. In addition to the U.S., bortezomib is approved in 27 European countries, South Korea, Argentina and Israel. Bortezomib was discovered by ProScript, a company subsequently acquired by Leukosite, which was in turn acquired by Millennium in 1999. In 2003, Millennium established an alliance with Ortho Biotech and its affiliate Janssen-Cilag, pursuant to which Millennium is responsible for commercialization of bortezomib in the U.S., while Ortho Biotech and Janssen-Cilag handle commercialization in Europe and the rest of the world, with the exception of Japan where Janssen commercializes the drug. Also under the agreement, Millennium, Ortho Biotech and Johnson & Johnson Pharmaceutical Research and Development will jointly take part in a global development program for bortezomib in the U.S., the E.U. and Japan. The program will investigate bortezomib for the treatment of multiple forms of solid and hematological cancers, including continued investment in multiple myeloma. Currently, approximately 80 clinical trials are under way. Bortezomib was assigned orphan drug designation in 2003 by the FDA for the treatment of multiple myeloma. In 2004, the FDA granted

bortezomib fast track designation for relapsed and refractory mantle cell lymphoma.

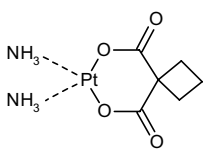
Capecitabine



Capecitabine (Xeloda®) is a pyrimidine antagonist that was launched by Roche in 1998 as a tablet formulation for the treatment of metastatic paclitaxel-resistant breast cancer, and again in 2001 for the treatment of colorectal and metastatic colorectal cancer. In 2003, the drug was launched by Chugai, Roche's Japanese subsidiary, for the treatment of breast cancer. It was registered in 2005 by Roche for the treatment of colon cancer. Currently, phase III clinical trials are in progress at Roche for the treatment of stomach cancer, and the NCI is conducting phase II trials for the treatment of pancreatic and rhinopharyngeal cancer. Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, 60-kDa carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme thymidine phosphorylase (dTHdPase), which is expressed in many tissues throughout the body and in some human carcinomas at higher levels than in surrounding normal tissues, then hydrolyzes 5'-DFUR to the active drug 5-FU.

Original monograph – Drugs Fut 1996, 21(4): 358.

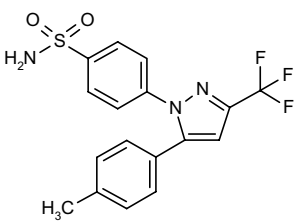
Carboplatin



The second-generation antineoplastic platinum complex carboplatin was originally launched in 1986 in the U.K. by Bristol-Myers Squibb for two indications: the treatment of small cell lung cancer and advanced ovarian cancer of epithelial origin. The NCI is currently conducting several phase III trials with carboplatin as monotherapy or in combination with other chemotherapy for the treatment of bladder, brain, kidney, endometrial and head and neck cancer, NSCLC, NHL, melanoma and retinoblastoma. Carboplatin as monotherapy or in combination with other chemotherapy is also the subject of several phase II trials being carried out by the NCI for the treatment of germ cell ovarian cancer, thymoma and thymic carcinoma. Phase II monotherapy trials are also being conducted at the NCI for the treatment of glioma and medulloblastoma. The National Cancer Institute of Canada is conducting phase II trials for salivary gland cancer. Carboplatin, one of the most widely used platinum anticancer drugs worldwide, forms preferential crosslinks with guanine in DNA, eventually causing cell death. The drug may also interact with nuclear proteins, and is non-phase-specific. Carboplatin was first synthesized in 1971 by Johnson Matthey and was developed over a 12-year period under a collaboration among Johnson Matthey, the Institute of Cancer Research and Bristol-Myers Squibb. At present, Johnson Matthey manufactures carboplatin for commercialization. In October 2004, the former American Pharmaceutical Partners, now Abraxis BioScience, received approval from the FDA for a generic equivalent of carboplatin injection (liquid form). The company already has a lyophilized form of the product on the market.

Original monograph – Drugs Fut 1983, 8(6): 489.

Celecoxib



Pfizer's celecoxib is a nonsteroidal antiinflammatory drug launched in 1999 in the U.S. for the treatment of rheumatoid arthritis, osteoarthritis and familial adenomatous polyposis. The drug was launched again by Pfizer in the U.S. in 2002 for the treatment of dysmenorrhea and pain, and was approved there for the treatment of ankylosing spondylitis in 2005. At present, Astellas Pharma is awaiting approval in Japan for the treatment of lower back pain. Celecoxib is in phase III clinical trials at Pfizer for the treatment of urethral colic, and at the European Organization for Research and Treatment of Cancer (EORTC) for the treatment of colorectal cancer. The drug is being studied extensively by the NCI, including phase III trials for the treatment of oral and salivary gland cancer, phase II/III trials for bladder cancer and actinic keratosis, phase II trials for the treatment of metastatic colorectal cancer, solid tumors, NSCLC (in collaboration with Cornell University) and glioblastoma multiforme, and phase I trials for the treatment of cancer-related cachexia. The National Institutes of Health (NIH) is evaluating the potential of the drug in phase II trials for the treatment of macular degeneration, and clinical trials are under way

at the M.D. Anderson Cancer Center for the treatment of lung cancer. The mechanism of action of celecoxib is believed to be inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, the compound does not inhibit the cyclooxygenase-1 (COX-1) isozyme. In animal colon tumor models, significant reduction of tumor multiplicity and incidence has been observed. Originally developed at Searle (now Pfizer), Yamanouchi (now Astellas Pharma) obtained rights to the drug pursuant to a co-development agreement signed in April 1996. In October 2000, celecoxib received orphan drug designation for the treatment of familial adenomatous polyposis. Currently, the drug is being distributed by Pfizer in Canada, France, Germany, Italy, the U.K. and the U.S.

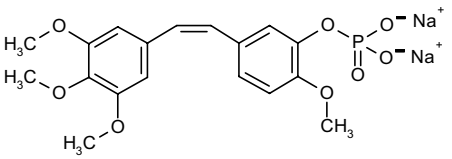
Original monograph – Drugs Fut 1997, 22(7): 711.

Cetuximab

Cetuximab is a chimeric monoclonal antibody (MAb) originally developed by ImClone and first launched in Switzerland in 2003 as Erbitux™ by partner Merck KGaA as monotherapy and in combination with irinotecan for the treatment of irinotecan-refractory metastatic colorectal cancer. In 2006, the product was commercialized in Switzerland for the treatment, alone or in combination with high-dose radiation, of patients with advanced squamous cell cancer of the head and neck (SCCHN). Approval for these indications has been obtained in the E.U. and many non-E.U. countries and the product is available in the U.S. and several European countries. Cetuximab is currently in advanced clinical development as monotherapy and/or in combination with other chemotherapies for the treatment of several indications, including colorectal cancer, NSCLC, pancreatic and stomach cancer. In addition, phase II trials of cetuximab are ongoing for the treatment of ovarian and breast cancer. Furthermore, Vanderbilt University is studying the potential of cetuximab for the treatment of Menetrier's disease. ImClone had been developing cetuximab for the treatment of prostate cancer but discontinued development of the antibody for this indication. Cetuximab binds to the extracellular domain of the epithelial growth factor receptor (EGFR, HER1, c-erbB1) on both normal and tumor cells and inhibits the binding of EGF and other ligands such as transforming growth factor-α (TGF-α), and thereby prevents signal transduction and tyrosine kinase autophosphorylation, resulting in inhibition of cell growth, induction of apoptosis and decreased matrix metalloproteinase and VEGF production. In 1998, Merck licensed worldwide rights to develop and market cetuximab outside the U.S. and Canada and co-exclusive rights to market cetuximab in Japan. In 2001, ImClone and Bristol-Myers Squibb established an agreement to co-develop and co-promote cetuximab in the U.S., Canada and Japan. In 2000, cetuximab was assigned orphan drug designation by the FDA for the treatment of SCCHN in patients who express the EGFR.

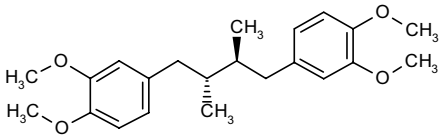
Original monograph – Drugs Fut 2000, 25(9): 895.

Combretastatin A-4 Phosphate



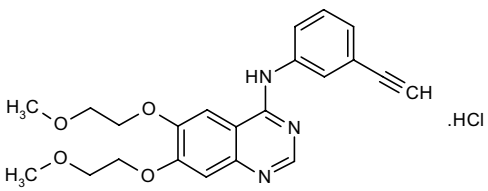
A phosphate prodrug of combretastatin A-4, combretastatin A-4 phosphate (CA4P) is a vascular targeting agent under development by OxiGene for several indications. CA4P, one of several compounds licensed from Arizona State University in 1997, was originally derived from the root bark of the *Combretum caffrum* tree, also known as the Cape bushwillow. CA4P, which is rapidly converted to the active compound in the bloodstream, enters the endothelial cells of tumor-associated blood vessels, where it affects the microtubules that form the cytoskeleton of the endothelial cells lining the tumor vasculature. When this tubulin structure is disrupted, the endothelial cells change shape from flat to round, stopping blood flow through the capillary, starving the tumor of nutrients and causing tumor cell death. This mechanism of action differentiates CA4P from angiogenesis inhibitors, which are designed to work by preventing the growth of sprouting new blood vessels. The company is evaluating CA4P in phase III trials in patients with inoperable stage IIIB/IV NSCLC, a subset of patients not deemed suitable for curative treatment with concurrent radiotherapy. OxiGene is studying CA4P in phase II trials as monotherapy for the treatment of anaplastic thyroid cancer. The company is also evaluating combination therapy of CA4P with other chemotherapeutic agents in phase I/II for the treatment of anaplastic thyroid and advanced ovarian cancer and in phase II for the treatment of breast and lung cancer. A phase I/II trial is under way with CA4P in combination with the iodine-labeled antibody A5B7 for the treatment of gastrointestinal and colorectal cancer. Additional phase I/II trials include CA4P in combination with radiotherapy for the treatment of head and neck cancer and prostate cancer and as monotherapy for the treatment of wet age-related macular degeneration (AMD). OxiGene is also evaluating the drug in early clinical studies as monotherapy for cervical cancer and in combination with carboplatin and paclitaxel for the treatment of solid tumors. Preclinical studies are under way at the company with CA4P in combination with bevacizumab for the treatment of colorectal cancer. In 2003, CA4P was granted orphan drug designation by the FDA for the treatment of anaplastic thyroid, medullary thyroid and stage IV papillary or follicular thyroid cancer. In 2006, the FDA granted orphan drug designation to CA4P for the treatment of ovarian cancer.

EM-1421



EM-1421, a new chemical entity derived semisynthetically from a desert plant, is currently in phase II clinical studies at Erimos Pharmaceuticals (formerly BioCure Medical) as intravaginal therapy for cervical intraepithelial neoplasia (CIN). In addition, the potential use of EM-1421 as intravenous therapy for the treatment of refractory and metastatic solid tumors that are unresponsive to conventional therapy is being evaluated in phase I clinical studies. A phase I trial with EM-1421 delivered by injection for the treatment of head and neck cancer was conducted by the company in collaboration with Duke University and the University of South Carolina. In addition, research is ongoing to develop an oral formulation of EM-1421. Erimos holds an exclusive license for nordihydroguaiaretic acid (NDGA) derivatives from Johns Hopkins University. NDGA is extracted from the resin of the leaves of *Larrea tridentata*, a desert plant indigenous to the southwestern U.S. and Mexico. EM-1421 is a small-molecule drug designed to target abnormal tumor cells while causing little or no toxicity to healthy cells.

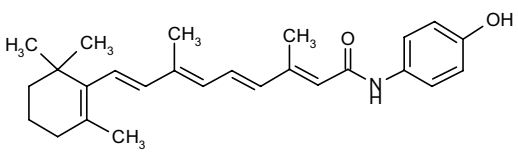
Erlotinib Hydrochloride



Erlotinib hydrochloride is an EGFR (erbB1) inhibitor launched by Genentech, OSI Pharmaceuticals and Roche in the U.S. in 2004 as Tarceva® for the oral treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In September 2005, Roche received approval in the E.U. for this indication, and 2 months later the FDA approved the drug for an additional indication: first-line treatment of pancreatic cancer in combination with gemcitabine in patients with locally advanced or metastatic disease who have not received previous chemotherapy. In the E.U., Roche has filed a marketing authorization application (MAA) for the treatment of pancreatic cancer. Erlotinib is designed to block tumor cell growth by inhibiting the tyrosine kinase activity of HER1/EGFR, thereby blocking the HER1/EGFR signaling pathway inside the cell. Phase III clinical trials are under way at Genentech, OSI and Roche to evaluate erlotinib as combination therapy for the treatment of relapsed NSCLC. Additional phase III trials are under way at Roche with erlotinib as monotherapy and in combination with bevacizumab as first- and second-line therapy, respectively, for NSCLC. The NCI, OSI and Genentech are evaluating the potential of the drug in phase II trials for head and neck cancer. The companies and the NCI are also conducting phase II trials for the treatment of glioblastoma multiforme. Phase II trials are ongoing at Genentech and Chugai for the treatment of kidney and lung cancer, respectively. The NCI is conducting several phase II trials to study the potential of erlotinib as monotherapy for the treatment of male breast, kidney, liver, esophageal and stomach cancer, glioma and sarcoma. Also at the NCI, erlotinib combination therapy is in phase II trials for the treatment of metastatic breast and prostate cancer. Phase I/II combination studies for the treatment of anaplastic astrocytoma and oligodendroglioma are also under way. Additional phase I/II clinical trials at the NCI are evaluating the drug for the treatment of ovarian cancer and early clinical trials are studying the drug's potential for the treatment of colorectal cancer, pediatric brain cancer, mouth cancer and solid tumors. Originally developed by Pfizer, erlotinib is being developed under an alliance established by OSI with Genentech and Roche. According to an agreement signed in 2001 by Genentech and OSI and amendments to the original agreement, OSI was responsible for obtaining FDA approval of the drug for the treatment of NSCLC. Genentech is in charge of the marketing, launch and promotion of erlotinib, while OSI is responsible for providing at least 25% of the combined U.S. sales force for the promotion of the product. The companies share responsibility for the ongoing development of erlotinib post-launch. OSI is responsible for commercial manufacturing and supply in the U.S.

Original monograph – Drugs Fut 2002, 27(10): 923.

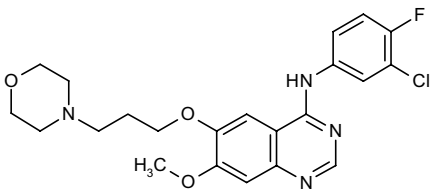
Fenretinide



Fenretinide, a novel synthetic retinoid, is currently undergoing phase II clinical development at the NCI for the treatment of prostate cancer. Early clinical studies are also under way to evaluate the compound for the treatment of ovarian cancer, head and neck cancer, Hodgkin's lymphoma, NHL, hematological malignancies and recurrent neuroblastoma. The compound was initially discovered through a collaboration between R.W. Johnson and the NCI.

Original monograph – Drugs Fut 1980, 5(3): 132.

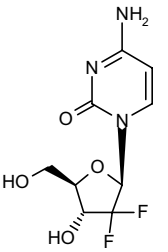
Gefitinib



An EGFR (erbB1) inhibitor that blocks the signal transduction pathways induced by EGFR, gefitinib was launched in 2002 in Japan as Iressa™ for the oral treatment of NSCLC. The drug was the first in a new class of anticancer drugs known as EGFR tyrosine kinase inhibitors to gain market approval and is currently available in a number of countries around the world, including the U.S., Japan, Canada and Australia. Gefitinib targets signaling pathways that appear to play a major role in the growth of many solid tumors and may therefore have therapeutic potential in a broad range of common cancers. In early 2005, AstraZeneca withdrew its MAA in the E.U. for gefitinib for the treatment of NSCLC based on disappointing results from ISEL (Iressa Survival Evaluation in Lung cancer), a phase III trial which failed to reach statistical significance compared with placebo in the overall trial population (the primary study endpoint). In spite of the MAA withdrawal, AstraZeneca continues the clinical development of gefitinib, including phase III trials in collaboration with the NCI for the treatment of head and neck cancer and phase II trials in combination with other chemotherapies for the treatment of metastatic breast cancer and esophageal cancer. Phase II trials are also under way at the company in patients with chemotherapy-refractory germ cell tumors expressing EGFR and for the treatment of adrenocortical carcinoma, liver cancer and small cell lung cancer. The NCI is evaluating gefitinib combination therapy for the treatment of male breast, colorectal and bladder cancer and glioblastoma, and as monotherapy for the treatment of gastrointestinal, ovarian, prostate and thyroid cancer. Phase II combination trials are also under way at the NCI for the treatment of children with brain stem gliomas and at St. Jude Children's Research Hospital for neuroblastoma. Early clinical trials of gefitinib as monotherapy for the treatment of pediatric solid tumors are also ongoing at the NCI. Phase II trials with gefitinib are being conducted at the EORTC for the treatment of metastatic breast cancer and synovial sarcoma, and at the M.D. Anderson Cancer Center and the NCI for the treatment of squamous cell carcinoma of the skin. The Dana-Farber Cancer Institute is evaluating gefitinib monotherapy for the treatment of AML and in combination with docetaxel for the treatment of pancreatic cancer.

Original monograph – Drugs Fut 2002, 27(4): 339.

Gemcitabine



The nucleoside analogue gemcitabine was first launched in 1995 by Lilly as Gemzar® for the treatment of NSCLC, metastatic NSCLC and pancreatic cancer, and a year later for metastatic pancreatic cancer. The drug was approved in the E.U. in 2003 and in the U.S. in 2004 as combination therapy with paclitaxel for the treatment of metastatic breast cancer and in 2004 it was commercialized for this indication in the U.S. and Italy. Gemcitabine is also marketed for the treatment of advanced bladder cancer. At present, gemcitabine combination therapy is the subject of a phase III trial at Lilly for the treatment of breast and ovarian cancer with different combination therapies than those currently approved for these indications. The Tel-Aviv Sourasky Medical Center is conducting additional phase III trials in combination with curcumin and celecoxib for the treatment of colorectal cancer. Gemcitabine in combination with docetaxel is being developed in early clinical trials by Lilly and sanofi-aventis for the treatment of hormone-refractory prostate cancer. The compound is in phase II development by the NCI for the treatment of rhinopharyngeal cancer, metastatic head and neck cancer, kidney cancer, lymphoma and malignant mesothelioma. The NCI is evaluating gemcitabine combination therapy in additional phase II trials for the treatment of sarcoma, chondrosarcoma and leiomyosarcoma. Phase I trials are also in progress at the NCI evaluating the potential of gemcitabine in the treatment of brain cancer and solid tumors. The National Cancer Institute of Canada, the NCI and the Dana-Farber Cancer Institute are conducting phase II trials for gemcitabine combination therapy in salivary gland cancer. Gemcitabine interferes with the processes of DNA production, thereby preventing cancer cells from replicating and thus slowing or stopping tumor growth.

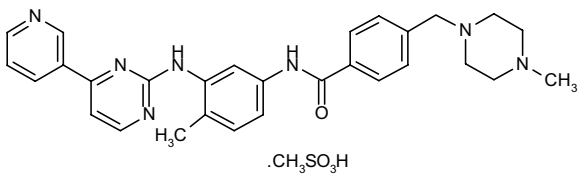
Original monograph – Drugs Fut 1990, 15(8): 794.

H-101

H-101 is a genetically engineered adenovirus developed at Shanghai Sunway Biotech and approved in 2005 in China in combination with chemotherapy as a treatment for patients with late-stage refractory nasopharyngeal cancer. The approval marked the first oncolytic viral therapy approved by any regulatory agency in the world. Phase II trials are also under way at the company to eval-

uate the drug's potential for the treatment of NSCLC, localized osteosarcoma and hematological/blood cancers. The deletion of an E1B-55kD segment in the virus results in its selective replication in and killing of tumor cells, while leaving normal cells unaffected.

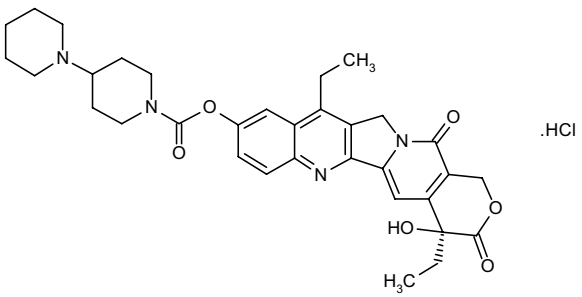
Imatinib Mesilate



Imatinib mesilate (Gleevec®, Glivec®) is a small-molecule tyrosine kinase inhibitor that was first launched in the U.S. in 2001 by Novartis for the treatment of patients with Philadelphia chromosome-positive (Ph^+) chronic myeloid leukemia (CML) in blast crisis, accelerated phase or in chronic phase after failure of interferon alfa therapy. The drug is indicated for the treatment of newly diagnosed adult and pediatric patients with Ph^+ CML in the E.U., Switzerland and several other countries. In Japan, imatinib is approved for adult patients in all phases of Ph^+ CML. At present, the drug has been cleared for marketing in over 80 countries for this indication. Imatinib is also approved in the E.U., the U.S. and other countries, including Japan, for the treatment of patients with Kit (CD117)-positive, unresectable and/or metastatic malignant gastrointestinal stromal tumors (GISTs). Regulatory applications have been filed in the U.S., the E.U. and Japan seeking approval for the treatment of adult patients with Ph^+ acute lymphoblastic leukemia (Ph^+ ALL). In 2005, Novartis filed for approval in the U.S. and the E.U. for two new indications: dermatofibrosarcoma protuberans and myeloproliferative diseases. Two additional indications, the treatment of hypereosinophilic syndrome and systemic mastocytosis, were also filed for approval in 2006. In terms of clinical development, imatinib as monotherapy is in phase III trials at Novartis for the treatment of hematological malignancies and astrocytoma. Imatinib in combination with hydroxyurea and/or temozolomide is also in phase III testing for glioblastoma multiforme. More than 15 phase II trials are under way for the treatment of several oncology indications, such as metastatic breast, colorectal, ovarian, prostate, small cell lung and head and neck cancer, Ewing's sarcoma and AIDS-related Kaposi's sarcoma, among others. The NCI is also conducting phase I/II trials of the drug as monotherapy for the treatment of oligodendroglioma and in combination with bevacizumab in patients with advanced melanoma. In 2001, imatinib was granted orphan drug designation by both the FDA and the EMEA for the treatment of CML. The drug was also granted orphan drug designation by the EMEA and the FDA in 2001 and 2002, respectively, for the treatment of GISTs. Additional FDA orphan drug designations have been assigned for the treatment of systemic mastocytosis without the D816V c-kit mutation and idiopathic hypereosinophilic syndrome, including acute and chronic eosinophilic leukemia. In Japan, the drug received orphan drug designation for the treatment of GISTs in 2002 and for the treatment of CML in 2000.

Original monograph – Drugs Fut 2001, 26(6): 545.

Irinotecan Hydrochloride



Originally developed by Yakult Honsha, irinotecan hydrochloride has been marketed for over 20 years by licensee Daiichi Pharmaceutical (now Daiichi Sankyo) for the treatment of lung cancer and cancers of the uterine cervix and ovaries. The drug, a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*, is an antineoplastic agent from the topoisomerase I inhibitor class. In Europe, irinotecan was first approved in France in 1995 for the second-line treatment of metastatic colorectal cancer after 5-FU failure. In the U.S., the drug was launched by licensee Pfizer in 1998 for the treatment of colorectal cancer and in 2000 for the treatment of metastatic colorectal cancer. In 2006, Daiichi withdrew a regulatory application seeking approval in Japan for the treatment of pancreatic cancer. At present, the compound is in phase III development at sanofi-aventis, another licensee, as monotherapy or in combination with chemotherapy for the treatment of colon cancer. Phase III clinical studies are also under way at Pfizer for the treatment of small cell lung cancer and stomach cancer. The NCI has a robust phase II development program for irinotecan, including trials for the treatment of bladder, breast and head and neck cancer, neuroblastoma, solid tumors, sarcoma and several other cancer indications. The EORTC is conducting phase II trials for the treatment of penile cancer.

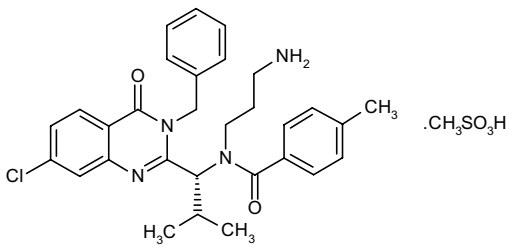
Original monograph – Drugs Fut 1987, 12(3): 207.

IRX-2

IRX-2, composed of a uniform, well-defined set of naturally derived cytokines, is IRX Therapeutics' lead anti-

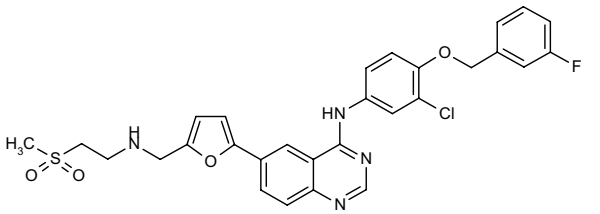
cancer therapy in phase II clinical development for the treatment of squamous cell carcinoma of the head and neck. Results from phase II trials suggest that IRX-2 stimulates T-cell-mediated antitumor activity.

Ispinesib Mesilate



Ispinesib mesilate (715992, SB-715992, CK-0238273) is a novel small-molecule oncology drug candidate directed against kinesin spindle protein (KSP) in phase II development by GlaxoSmithKline for the treatment of breast and ovarian cancer and NSCLC. The NCI is evaluating ispinesib in early clinical development for the treatment of AML, CML, ALL and advanced myelodysplasia, and in phase II trials for the treatment of advanced or metastatic colorectal cancer, locally advanced, recurrent or metastatic hepatocellular carcinoma and melanoma. The NCI is conducting phase II trials for the second-line treatment of patients with hormone-refractory prostate cancer and for head and neck cancer, as well as early clinical trials for the treatment of solid tumors in patients who have failed to respond to all standard therapies. Ispinesib, a targeted antimitotic agent, is the first drug candidate to emerge from a collaboration between Cytokinetics and GSK established in 2001 to discover, develop and commercialize novel small-molecule therapeutics for the treatment of cancer and other diseases. Specifically, the companies are developing therapeutics directed against human mitotic kinesins, a newly characterized family of cytoskeletal enzymes which are essential to mitotic spindle formation and function during cell division. Inhibition of mitotic kinesin function disrupts the cell cycle and leads to cell death. Cytokinetics initiated drug discovery activities in the area of kinesin inhibition in 1998. These next-generation antimitotics have the potential to exhibit an improved therapeutic profile over existing antimitotic drugs. Pursuant to the alliance between Cytokinetics and GSK, the latter is responsible for worldwide development and commercialization of ispinesib, as well as other products arising under the collaboration, while Cytokinetics retains a product-by-product option to co-fund certain development activities. Therapeutic targets identified during the duration of the collaboration may revert to Cytokinetics for independent research and development, with GSK retaining an option to resume joint activities.

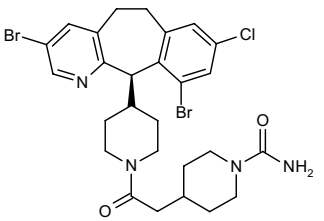
Lapatinib



Lapatinib (Tykerb®), a dual erbB1 and erbB2 kinase inhibitor in development at GlaxoSmithKline, is currently undergoing phase III clinical trials for the oral treatment of metastatic breast cancer. The compound is also being evaluated in the treatment of brain, gallbladder, prostate, ovarian, renal, endometrial, hepatobiliary and head and neck cancers in collaboration with the NCI. Lapatinib was granted fast track status by the FDA in 2005 for the treatment of refractory advanced or metastatic breast cancer patients who have documented erbB2 overexpression and who have failed previous therapy.

Original monograph – Drugs Fut 2005, 30(12): 1225.

Lonafarnib



An apoptosis inducer and farnesyltransferase inhibitor, lonafarnib (Sch-66336, Sarasar®) is in phase III clinical development at Schering-Plough for the treatment of myelodysplasia and CML. Phase II clinical trials are also ongoing at the company for the oral treatment of breast cancer and other solid tumors. Additional phase II trials are evaluating lonafarnib in combination with paclitaxel/carboplatin for the treatment of ovarian cancer. The drug candidate is in early clinical development for the treatment of head and neck cancer at the NCI and for the treatment of astrocytoma, oligodendroglioma and brain cancer at the EORTC. A phase II study is under way to determine the potential of lonafarnib in combination with paclitaxel and carboplatin for the treatment of ovarian cancer.

Original monograph – Drugs Fut 2003, 28(12): 1168.

Lontucirev (Replicating Adenovirus)

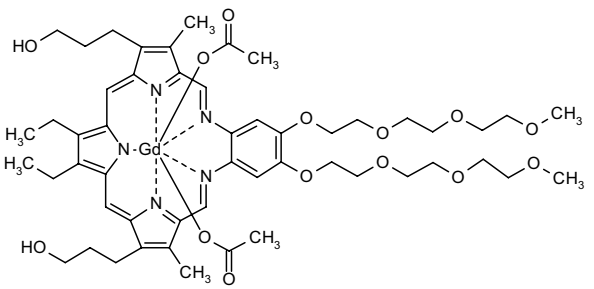
Lontucirev (replicating adenovirus) (ONYX-015), a specially modified virus discovered at Onyx, is currently being evaluated by the NCI in phase I clinical trials in

combination with cisplatin and 5-FU for the treatment of advanced squamous cell cancer of the head and neck.

Lovaxin C

Lovaxin C, a *Listeria*-based therapeutic cancer vaccine, is in phase I/II clinical trials at Advaxis for the treatment of cervical cancer. Early clinical studies are also under way for the treatment of head and neck cancer. Vaccines based upon *Listeria* have a potent, direct stimulatory effect on tumor-killing T-cells. Lovaxin C is one of several *Listeria* cancer vaccines based on vaccine technology originated at the University of Pennsylvania and under development at Advaxis.

Motexafin Gadolinium



Motexafin gadolinium (Xcytrin®) is an apoptosis inducer being studied at Pharmacyclics for the treatment of a wide variety of cancer indications. Phase III trials are under way for the treatment of brain metastases from NSCLC in combination with whole-brain radiation therapy (WBRT). Phase II trials are ongoing to test motexafin gadolinium alone or in combination with chemotherapy or radiation for the treatment of renal cell carcinoma, NSCLC, glioblastoma multiforme, CLL, NHL and multiple myeloma, while early clinical trials at Pharmacyclics are testing the drug candidate's potential in the treatment of anaplastic astrocytoma, pediatric brain tumors, head and neck cancer and advanced solid tumors. After administration, motexafin gadolinium selectively localizes and accumulates inside cancer cells, where it disrupts cellular metabolism, interferes with the flow of energy and ultimately causes apoptosis, leading to the selective destruction of cancer cells. Preclinical studies have shown that motexafin gadolinium enhances the efficacy of radiation therapy and several commonly used chemotherapeutic agents such as doxorubicin, rituximab, ibritumomab tiuxetan and docetaxel. In December 2003, the drug was granted fast track designation by the FDA for the treatment of brain metastases in NSCLC patients.

Multikine®

Multikine® (buffy coat interleukins, BC-IL), a mixture of naturally occurring cytokines, including interleukins, interferons, chemokines and colony-stimulating factors (CSF), is in clinical development at Cel-Sci for the treatment of advanced primary head and neck cancer. Phase II trials are under way for the treatment of oral squamous cell carcinoma. The immunotherapeutic agent is nontoxic and offers a diverse and possibly synergistic cytokine profile believed to play an important role in local, regional and possibly systemic immune restoration. Orient EuroPharma is Cel-Sci's Multikine® partner in Asia.

Nimotuzumab

Nimotuzumab, a humanized IgG_1 monoclonal antibody targeting the EGFR, is currently undergoing phase III clinical trials in combination with radiation for the treatment of children with diffuse, intrinsic pontine (brain stem) glioma. Phase II clinical trials for the treatment of astrocytoma, metastatic pancreatic cancer, rhinopharyngeal cancer and glioblastoma are also under way. Early clinical trials are also ongoing for the treatment of NSCLC. In 2004, the compound received orphan drug designation in the E.U. and the U.S. for the treatment of glioma. Originally discovered by the Center of Molecular Immunology, nimotuzumab was licensed to YM BioSciences for the major countries, including Europe, North America and the Pacific Rim countries, excluding China where Biotech Pharmaceuticals holds rights. Biocon Biopharmaceuticals was granted rights to the product in India. In 2003, YM BioSciences licensed rights to nimotuzumab for cancer indications to Oncoscience in Europe. In 2005, YM BioSciences' CIMYM subsidiary partnered with Kuhnil Pharmaceutical to expand the development program for nimotuzumab for the treatment of NSCLC in Korea. Early clinical studies are under way for this indication.

Original monograph – Drugs Fut 2003, 28(9): 847.

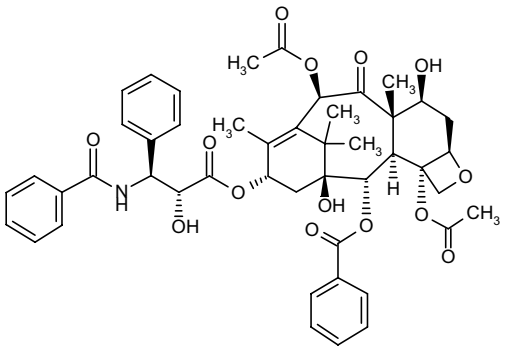
OncoVEX$^{GM\text{-}CSF}$

The oncolytic virus OncoVEX$^{GM\text{-}CSF}$ is a therapeutic vaccine developed at BioVex that selectively kills tumor cells and also induces tumor cells to secrete the immune stimulator granulocyte-macrophage colony-stimulating factor (GM-CSF), potentially enhancing the destruction of both injected and metastatic tumor deposits. Phase I/II clinical trials of the vaccine have been completed in several solid tumors, including breast and gastrointestinal cancer. Phase II trials are under way at BioVex for the treatment of malignant melanoma and head and neck cancer. Once marketed, OncoVEX$^{GM\text{-}CSF}$ is expected to be administered in combination with standard cancer therapies, such as chemotherapy or radiotherapy.

p53-DC Vaccine

The p53-DC vaccine consists of autologous dendritic cells loaded with a cocktail of three wild-type (R9V, L9V, G11V) and three modified (S9Vm, K9Vm, Y9Lm) HLA-A2-binding p53 peptides and a pan-MHC class II peptide (PADRE). Currently, the drug candidate is undergoing phase I/II clinical trials at the University of Copenhagen and the Herlev University Hospital for the treatment of breast cancer. Additional phase I/II trials are being conducted by the NCI for the treatment of extensive-stage small cell lung cancer in combination with chemotherapy. Early clinical trials at the University of Pittsburgh are evaluating the potential of the p53-DC vaccine to treat head and neck cancer. The compound was jointly discovered under a collaboration between Herlev University Hospital, Roskilde Hospital and the University of Copenhagen.

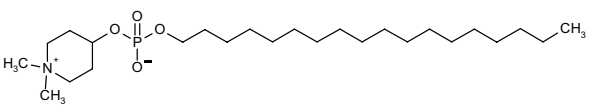
Paclitaxel



Paclitaxel is a microtubule-stabilizing agent belonging to the chemical class of taxanes, originally obtained from the yew tree. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Furthermore, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. Discovered in 1963 as part of an NCI program to screen plant species for anticancer activity, clinical studies with paclitaxel began in 1983. In 1991, Bristol-Myers Squibb was selected by the NCI as a commercial partner in developing Taxol® (paclitaxel injection) and signed a CRADA with the NCI. Taxol® was first approved in December 1992 by the FDA for the treatment of both refractory breast and ovarian cancer and was launched in the U.S. by Bristol-Myers Squibb the following year. In 1994, Bristol-Myers Squibb launched Taxol® in the U.S. for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, with the stipulation that prior therapy should have included an anthracycline unless clinically contraindicated. Also, a 3-h infusion schedule in ovarian and breast cancer patients was approved. Other approved indications for Taxol® include the treatment of NSCLC in combination with cisplatin where surgery or radiation is inappropriate, the treatment of stomach cancer and the second-line treatment of AIDS-related Kaposi's sarcoma. In 2005, Bristol-Myers Squibb received approval for Taxol® in Japan for the treatment of uterine cancer. Phase II development is being undertaken at the NCI for the treatment of thymoma and thymic carcinoma, esophageal cancer, head and neck cancer (with BMS) and renal carcinoma. Xorane, Ivax's patented oral formulation of paclitaxel is also in phase II clinical trials for the treatment of breast cancer, gastric cancer and NSCLC. Bristol-Myers Squibb is developing an oral formulation of paclitaxel in early clinical trials for the treatment of sarcoma, NSCLC and prostate cancer. Adventrx Pharmaceuticals is evaluating a paclitaxel nanoemulsion formulation in preclinical studies. In terms of nononcological indications for paclitaxel, Angiotech is evaluating the drug in phase II clinical trials for the treatment of rheumatoid arthritis. In June 2005, Angiotech established a license agreement allowing Broncus Technologies to incorporate Angiotech's paclitaxel technology with Broncus's Exhale® system to treat emphysema. The worldwide, nonexclusive license relates to chronic obstructive pulmonary disease (COPD)-related diseases. Broncus expects to begin phase III trials with this implant in 2006.

Original monograph – Drugs Fut 1986, 11(1): 45.

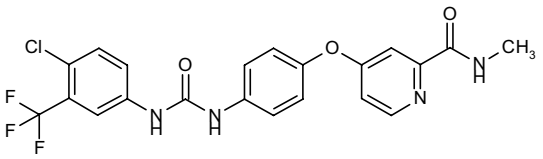
Perifosine



Perifosine is an oral alkylphosphocholine protein kinase B (PKB/Akt) inhibitor with antitumor properties mediated by disruption of lipid-mediated signal transduction pathways, including mitogen-activated protein kinase (MAPK) and c-Jun *N*-terminal kinase (JNK), required for tumor cell growth and survival. The compound has demonstrated potent preclinical antitumor activity both *in vitro* and *in vivo* and is able to potentiate the antitumor effects of radiotherapy and several commonly used chemotherapeutic agents. An extensive phase II clinical program is currently under way, including trials conducted by AEterna Zentaris and Keryx. Pursuant to a CRADA, the NCI is conducting several trials as well. Indications under evaluation include melanoma, sarcoma, multiple myeloma, refractory NSCLC, breast cancer (male and female), pancreatic cancer, head and neck cancer, prostate cancer, renal cell carcinoma and other solid tumors.

Original monograph – Drugs Fut 2000, 25(12): 1257.

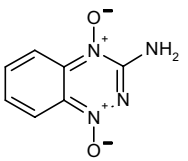
Sorafenib



Sorafenib (Bay-43-9006, Nexavar®), an oral multikinase inhibitor that targets serine/threonine and receptor tyrosine kinases in both the tumor cell and tumor vasculature, was approved in the U.S. in 2005 for the treatment of advanced metastatic renal cell carcinoma. Approval has also been obtained in Switzerland and a positive opinion was received in the E.U. for this indication. Filings have also been completed in Australia, Brazil, Canada and Mexico. Sorafenib, co-developed by Bayer and Onyx, has been studied in more than 20 tumor types and in more than 4,000 patients to date. In terms of clinical development, the drug is being jointly developed by Bayer and Onyx in phase III trials as a single agent for the treatment of advanced hepatocellular carcinoma and in combination with carboplatin and paclitaxel in patients with advanced metastatic melanoma. The companies are also conducting phase II trials in combination with doxorubicin for the treatment of advanced hepatocellular carcinoma. Additional phase II trials are ongoing for NSCLC and in postmenopausal women with estrogen receptor- and/or progesterone receptor-positive metastatic breast cancer. In addition, the NCI is evaluating the compound both as monotherapy and in combination with other oncology agents in phase II trials for several indications, including metastatic breast cancer, head and neck cancer, NSCLC, ovarian, pancreatic, prostate, uterine, thyroid and gallbladder cancer and malignant mesothelioma, as well as multiple myeloma. An NCI-sponsored phase I trial is ongoing for the treatment of anaplastic astrocytoma and glioma, including glioblastoma. Orphan drug status was granted by the FDA and the EMEA for the treatment of renal cell carcinoma in 2004, and orphan drug designation was assigned in both the U.S. and the E.U. for the treatment of advanced hepatocellular carcinoma in 2006. Fast track designation was assigned in the U.S. for the treatment of metastatic liver cancer.

Original monograph – Drugs Fut 2002, 27(12): 1141.

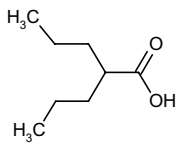
Tirapazamine



Tirapazamine (Tirazone®) is a hypoxia-selective cytotoxin that is currently undergoing phase III clinical trials at sanofi-aventis for the treatment of head and neck cancer. It is also being evaluated at the NCI for the treatment of cervical and small cell lung cancer, NSCLC and pediatric rhabdomyosarcoma.

Original monograph – Drugs Fut 1995, 20(3): 256.

Valproic Acid



Valproate, available as valproic acid, its salt and esters, is an antiepileptic agent used for the treatment of both generalized and partial seizures in adults and children. The antiepileptic properties of valproic acid, which is structurally unrelated to other antiepileptic drugs, were discovered 1963 and the drug was first marketed in France in 1967 and introduced in the U.S. by Abbott in 1978 in a liquid-filled capsule formulation. In terms of clinical studies, phase III trials are under way with valproate in combination with *all-trans*-retinoic acid and chemotherapy for the treatment of AML. Early clinical trials are under way at the NCI for the treatment of HIV-related Kaposi's sarcoma, childhood meningioma, recurrent or refractory solid tumors and recurrent or refractory brain cancer, and in combination with decitabine for NHL and NSCLC. The M.D. Anderson Cancer Center is studying the compound in combination with decitabine for myelodysplasia. Early clinical trials are also ongoing at Johns Hopkins University for use in the treatment of nasopharyngeal carcinoma.

VB4-845

Viventia Biotech is conducting phase II trials with VB4-845, a targeted therapeutic consisting of the cytotoxic protein payload *Pseudomonas* exotoxin with a monoclonal antibody that targets epidermal cell adhesion molecule (EpCAM), as a treatment for advanced, recurrent head and neck cancer. Phase I/II clinical trials are also under way at the company for the treatment of recurrent bladder cancer. Originally developed at the University of Zurich, the compound is exclusively licensed to Viventia. VB4-845 received orphan drug designation in the U.S. and in Europe for the treatment of head and neck cancer in 2005.

Zalutumumab

Zalutumumab (HuMax-EGFR), a fully human, high-affinity antibody targeted at the EGFR, is currently undergoing phase I/II clinical trials at Genmab for the treatment

of head and neck cancer. In January 2006, zalutumumab was assigned fast track status for the treatment of patients with head and neck cancer who have previously failed standard therapies. In preclinical studies, zalutumumab eradicated tumors at very low and infrequent doses, especially when compared to other antibodies directed to EGFR. Medarex holds an equity interest in Genmab.