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Update 2006 – Treatment of Breast Cancer

(Source: Prous Science Integrity®)

Treatment of Breast Cancer by Drug

Drug	Target	Phase	Source
ABI-007	Tubulin	L-2005	Abraxis BioScience
ABIO-05/01		I	Abiogen
ABT-751[2]	Tubulin	II	Abbott
ActiVin®		I	National Cancer Institute (US)
Adecatumumab	Epithelial cell adhesion molecule (Ep-CAM)	II	Micromet/Serono
Advexin®		II	Introgen
AE-37	HER2/neu/erbB2	I	Antigen Express
AMG-706	Vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)	I	Amgen
Amonafide[2]	DNA topoisomerase II	II	ChemGenex
AN-152	DNA topoisomerase II, Gonadotropin-releasing factor hormone receptor (GnRH, LHRH)	I	AEterna Zentaris
Antineoplaston A10[2]	DNA	II	Burzynski Research Institute
Antineoplaston AS2-1[2]		II	Burzynski Research Institute
Arsenic trioxide[1]		II	University of Texas System
Arzoxifene hydrochloride[2]	Estrogen receptor (ER)	III	Lilly
Atamestane[2]	Aromatase (CYP19A1)	III	Intarcia
Axitinib	Vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)	II	Pfizer
AZD-2171	Vascular endothelial growth factor receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4)	II	National Cancer Institute (US)
Bevacizumab[1,2]	Vascular endothelial growth factor (VEGF)	Prereg.	Genentech/Roche
Bexarotene[1]	Retinoid X receptor (RXR)	II	National Cancer Institute (US)
BN-83495	Steryl sulfatase	I	Ipsen
Bortezomib[1]	Proteasome	II	Millennium
BrevaRex®	MUC1 (CD227 antigen)	I/II	ViRexx
BZL-101	Apoptosis-inducing factor-1 (AIF-1)	I/II	Bionovo
CEA-TRICOM	Carcinoembryonic antigen (CEA, CD66e)	I/II	National Cancer Institute (US)
Cetuximab[1]		II	Bristol-Myers Squibb/National Cancer Institute (US)
CoFactor™		I/II	Adventrx
Combretastatin A-4 phosphate[2]	Tubulin	II	OxiGene
CP-724714	HER2/neu/erbB2	I	OSI Pharmaceuticals
Diflomotecan	DNA topoisomerase I	II	Ipsen
E-7389	Tubulin	II	Eisai
ECO-04601	Peripheral benzodiazepine receptor (PBR)	IND filed	Ecopia
Edotecarin	DNA topoisomerase I	II	National Cancer Institute (US)
Erlotinib hydrochloride[1,2]	Epidermal growth factor receptor (EGFR, HER1, erbB1)	II	National Cancer Institute (US)
Ertumaxomab	HER2/neu/erbB2	II	Trion Pharma/Fresenius
Estetrol	Estrogen receptor α (ERα)	I/II	Pantarhei Bioscience
Everolimus[1,2]	Mammalian target of rapamycin (mTOR)	II	Novartis

Continuation

Treatment of Breast Cancer by Drug

Drug	Target	Phase	Source
Fosfluridine tidoxil		II	Heidelberg Pharma
Gefitinib[1,2]	Epidermal growth factor receptor (EGFR, HER1, erbB1)	II	AstraZeneca/National Cancer Institute (US)
GTI-2040	Ribonucleoside-diphosphate reductase	II	Lorus Therapeutics/National Cancer Institute (US)
Imatinib mesilate[1,2]	Platelet-derived growth factor receptor α (PDGFRα), Abl kinase, Kit (c-Kit)	II	National Cancer Institute (US)/Novartis
IMC-18F1		I	ImClone
Imexon[2]		I/II	AmpliMed
Imidacrine dihydrochloride[2]	DNA topoisomerase II	II	Xanthus
Indisulam	Cyclin-dependent kinase 2 (CDK2)	Discontinued	Eisai
INGN-225	p53	I/II	Introgen
INGN-241	Interleukin-24 (IL-24)	I/II	Introgen
INX-0125	Tubulin	IND filed	Inex/Hana Biosciences
Ipilimumab[2]	CTLA-4 (CD152)	II	Medarex/Bristol-Myers Squibb
Irinotecan hydrochloride[1,2]	DNA topoisomerase I	II	Pfizer/National Cancer Institute (US)
Ispinesib mesilate	Kinesin-like spindle protein (KSP, Eg5)	II	GlaxoSmithKline/Cytokinetics
Ixabepilone	Tubulin	III	Bristol-Myers Squibb
KOS-862 (R-1492)	Tubulin	II	Kosan Biosciences/Roche
KOS-953	Heat shock protein 90 (Hsp90)	II	Kosan Biosciences/National Cancer Institute (US)
KU-59436	NAD+ ADP-ribosyltransferase (poly[ADP-ribose]polymerase, PARP)	I	Kudos Pharmaceuticals (AstraZeneca)
Labetuzumab	CEA (CD66e)	I/II	Immunomedics
Lapatinib[2]	Epidermal growth factor receptor (EGFR, HER1, erbB1), HER2 (erbB2)	III	GlaxoSmithKline
Lapuleucel-T	HER2/neu/erbB2	I	Dendreon
Larotaxel dihydrate	Tubulin	II/III	Sanofi-Aventis/National Cancer Institute (US)
Lasofoxifene tartrate[2]	Estrogen receptor (ER)	III	Ligand/Pfizer
Lobaplatin[2]	DNA	II	AEterna Zentaris
Lobaplatin[2]	DNA	R-1998 (CN)	Hainan Chang An
Lonafarnib[2]	Farnesyltransferase	II	Schering-Plough
MetXia®		I/II	Oxford BioMedica
MKC-1		II	EntreMed
Mycograb®	Heat shock protein 90 (Hsp90)	I/II	NeuTec
OGX-011 (ISIS-112989)	Clusterin	II	OncoGeneX Technologies/Isis Pharmaceuticals
OncoVEX$^{GM\text{-}CSF}$		I/II	BioVex
OPT-22		I	Optimer Pharmaceuticals
Ortataxel[2]	Tubulin	II	Bayer/Indena
p53-DC Vaccine	p53	I/II	Herlev University Hospital/University of Copenhagen
PD-325901	Mitogen-activated protein/extracellular signal-related protein kinase (MEK)	I/II	Pfizer
Pemetrexed disodium[1,2]	Thymidylate synthase, dihydrofolate reductase, glycinamide transformylase formyltransferase	II	Lilly
Perifosine[2]	Protein kinase B (PKB/Akt)	II	Keryx/National Cancer Institute (US)/AEterna Zentaris
Pertuzumab	HER2/neu/erbB2	II	Roche/National Cancer Institute (US)
PV-10		I	Provectus
PX-104.1	HER2/neu/erbB2	II	Pharmexa
R-1550	MUC1 (CD227 antigen)	I	Roche
Raloxifene hydrochloride[1,2]	Estrogen receptor (ER)	III	Lilly/National Cancer Institute (US)
Ranpirnase	RNA	II (planned)	Alfacell
rhIGFBP-3	Insulin-like growth factor-I (IGF-I)	I	Insmed
Sabarubicin hydrochloride	DNA topoisomerase II	II	Menarini
Satraplatin	DNA	II	GPC Biotech
SaveCream®	Aromatase (CYP19A1)	II	Medical Discoveries
Sorafenib[1,2]	Vascular endothelial growth factor receptors VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4), platelet-derived growth factor receptor β (PDGFRβ)/Kit (c-Kit)/Flt-3 (Flk-2/Stk1), Raf kinase	II	National Cancer Institute (US)

Continuation

Treatment of Breast Cancer by Drug

Drug	Target	Phase	Source
Sulindac[1]		I	National Cancer Institute (US)
Sunitinib malate[2]	Vascular endothelial growth factor receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), platelet-derived growth factor receptor β (PDGFRβ)/Flt-3 (Flk-2/Stk1)	II	Pfizer
TAS-108	Estrogen receptor (ER)	II (US)	Taiho
TAS-108		I (JP)	Taiho
Temsirolimus[2]	Mammalian target of rapamycin (mTOR)	Discontinued	Wyeth
Tesmilifene hydrochloride[2]	Estrogen receptor (ER), histamine receptor	III	YM BioSciences
Theratope®	Sialyl-Tn	III (on hold)	Biomira
Tipifarnib[2]	Farnesyltransferase	II	National Cancer Institute (US)
Tocosol™ Paclitaxel[2]	Tubulin	III	Sonus/Schering AG
TPI-287	Tubulin	I	Tapestry Pharmaceuticals
Trabectedin[2]		II	PharmaMar/Johnson & Johnson
Trastuzumab-DM1	Tubulin, HER2/neu/erbB2	IND filed	ImmunoGen/Genentech
Triapine®	Ribonucleoside-diphosphate reductase	II	National Cancer Institute (US)
TSU-68	Vascular endothelial growth factor receptor-2 (VEGFR-2, Flk-1/KDR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR)	II	Taiho
Vatalanib succinate	Vascular endothleial growth factor receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4)	II	Novartis
Vinflunine[2]	Tubulin	II	Bristol-Myers Squibb
Vorinostat	Histone deacetylase	II	National Cancer Institute (US)
XRP-6258	Tubulin	II	Sanofi-Aventis
ZK-230211	Progesterone receptor (PR)	I	Berlex (Schering AG)/Jenapharm
ZK-EPO	Tubulin	II	Schering AG (Berlex)

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

Treatment of Breast Cancer by Source

Source	Drug	Target	Phase
Abbott	ABT-751[2]	Tubulin	II
Abiogen	ABIO-05/01		I
Abraxis BioScience	ABI-007	Tubulin	L-2005
Adventrx	CoFactor™		I/II
AEterna Zentaris	Lobaplatin[2]	DNA	II
	Perifosine[2]	Protein kinase B (PKB/Akt)	II
	AN-152	DNA topoisomerase II, Gonadotropin-releasing factor hormone receptor (GnRH, LHRH)	I
Alfacell	Ranpirnase	RNA	II (planned)
Amgen	AMG-706	Vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)	I
AmpliMed	Imexon[2]		I/II
Antigen Express	AE-37	HER2/neu/erbB2	I
AstraZeneca	Gefitinib[1,2]	Epidermal growth factor receptor (EGFR, HER1, erbB1)	II
Bayer	Ortataxel[2]	Tubulin	II
Berlex (Schering AG)	ZK-230211	Progesterone receptor (PR)	I
Biomira	Theratope®	Sialyl-Tn	III (on hold)
Bionovo	BZL-101	Apoptosis-inducing factor-1 (AIF-1)	I/II
BioVex	OncoVEX^{GM-CSF}		I/II
Bristol-Myers Squibb	Ixabepilone	Tubulin	III
	Cetuximab[1]		II
	Ipilimumab[2]	CTLA-4 (CD152)	II
	Vinflunine[2]	Tubulin	II
Burzynski Research Institute	Antineoplaston A10[2]	DNA	II
	Antineoplaston AS2-1[2]		II
ChemGenex	Amonafide[2]	DNA topoisomerase II	II
Cytokinetics	Ispinesib mesilate	Kinesin-like spindle protein (KSP, Eg5)	II
Dendreon	Lapuleucel-T	HER2/neu/erbB2	I
Ecopia	ECO-04601	Peripheral benzodiazepine receptor (PBR)	IND filed
Eisai	E-7389	Tubulin	II
Eisai	Indisulam	Cyclin-dependent kinase 2 (CDK2)	Discontinued
EntreMed	MKC-1		II
Fresenius	Ertumaxomab	HER2/neu/erbB2	II
Genentech	Bevacizumab[1,2]	Vascular endothelial growth factor (VEGF)	Prereg.
	Trastuzumab-DM1	Tubulin, HER2/neu/erbB2	IND filed
GlaxoSmithKline	Lapatinib[2]	Epidermal growth factor receptor (EGFR, HER1, erbB1), HER2 (erbB2)	III
	Ispinesib mesilate	Kinesin-like spindle protein (KSP, Eg5)	II
GPC Biotech	Satraplatin	DNA	II
Hainan Chang An	Lobaplatin[2]	DNA	R-1998 (CN)
Hana Biosciences	INX-0125	Tubulin	IND filed
Heidelberg Pharma	Fosfluridine tidoxil		II
Herlev University Hospital	p53-DC vaccine	p53	I/II
ImClone	IMC-18F1		I
ImmunoGen	Trastuzumab-DM1	Tubulin, HER2/neu/erbB2	IND filed
Immunomedics	Labetuzumab	CEA (CD66e)	I/II
Indena	Ortataxel[2]	Tubulin	II
Inex	INX-0125	Tubulin	IND filed
Insmed	rhIGFBP-3	Insulin-like growth factor-I (IGF-I)	I
Intarcia	Atamestane[2]	Aromatase (CYP19A1)	III
Introgen	Advexin®		II
	INGN-225	p53	I/II
	INGN-241	Interleukin-24 (IL-24)	I/II
Ipsen	Diflomotecan	DNA topoisomerase I	II
	BN-83495	Steryl sulfatase	I
Isis Pharmaceuticals	OGX-011 (ISIS-112989)	Clusterin	II
Jenapharm	ZK-230211	Progesterone receptor (PR)	I
Johnson & Johnson	Trabectedin[2]		II
Keryx	Perifosine[2]	Protein kinase B (PKB/Akt)	II
Kosan Biosciences	KOS-862 (R-1492)	Tubulin	II
	KOS-953	Heat shock protein 90 (Hsp90)	II

Continuation

Treatment of Breast Cancer by Source

Source	Drug	Target	Phase
Kudos Pharmaceuticals (AstraZeneca)	KU-59436	NAD+ ADP-ribosyltransferase (poly[ADP-ribose]polymerase, PARP)	I
Ligand	Lasofoxifene tartrate[2]	Estrogen receptor (ER)	III
Lilly	Arzoxifene hydrochloride[2]	Estrogen receptor (ER)	III
	Raloxifene hydrochloride[1,2]	Estrogen receptor (ER)	III
	Pemetrexed disodium[1,2]	Thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase	II
Lorus Therapeutics	GTI-2040	Ribonucleoside-diphosphate reductase	II
Medarex	Ipilimumab[2]	CTLA-4 (CD152)	II
Medical Discoveries	SaveCream®	Aromatase (CYP19A1)	II
Menarini	Sabarubicin hydrochloride	DNA topoisomerase II	II
Micromet	Adecatumumab	Epithelial cell adhesion molecule (Ep-CAM)	II
Millennium	Bortezomib[1]	Proteasome	II
National Cancer Institute (US)	Raloxifene hydrochloride[1,2]	Estrogen receptor (ER)	III
	Larotaxel dihydrate	Tubulin	II/III
	AZD-2171	Vascular endothelial growth factor receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4)	II
	Bexarotene[1]	Retinoid X receptor (RXR)	II
	Cetuximab[1]		II
	Edotecarin	DNA topoisomerase I	II
	Erlotinib hydrochloride[1,2]	Epidermal growth factor receptor (EGFR, HER1, erbB1)	II
	Gefitinib[1,2]	Epidermal growth factor receptor (EGFR, HER1, erbB1)	II
	GTI-2040	Ribonucleoside-diphosphate reductase	II
	Imatinib mesilate[1,2]	Platelet-derived growth factor receptor α (PDGFRα), Abl kinase, Kit (c-Kit)	II
	Irinotecan hydrochloride[1,2]	DNA topoisomerase I	II
	KOS-953	Heat shock protein 90 (Hsp90)	II
	Perifosine[2]	Protein kinase B (PKB/Akt)	II
	Pertuzumab	HER2/neu/erbB2	II
	Sorafenib[1,2]	VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4), platelet-derived growth factor receptor β (PDGFRβ)/Kit (c-Kit)/Flt-3 (Flk-2/Stk1), Raf kinase	II
	Tipifarnib[2]	Farnesyltransferase	II
	Triapine®	Ribonucleoside-diphosphate reductase	II
	Vorinostat	Histone deacetylase	II
	CEA-TRICOM	Carcinoembryonic antigen (CEA, CD66e)	I/II
	ActiVin®		I
	Sulindac[1]		I
NeuTec	Mycograb®	Heat shock protein 90 (Hsp90)	I/II
Novartis	Everolimus[1,2]	Mammalian target of rapamycin (mTOR)	II
	Imatinib mesilate[1,2]	Platelet-derived growth factor receptor α (PDGFRα), Abl kinase, Kit (c-Kit)	II
	Vatalanib succinate	Vascular endothleial growth factor receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4)	II
OncoGeneX Technologies	OGX-011 (ISIS-112989)	Clusterin	II
Optimer Pharmaceuticals	OPT-22		I
OSI Pharmaceuticals	CP-724714	HER2/neu/erbB2	I
Oxford BioMedica	MetXia®		I/II
OxiGene	Combretastatin A-4 phosphate[2]	Tubulin	II
Pantarhei Bioscience	Estetrol	Estrogen receptor α (ERα)	I/II
Pfizer	Lasofoxifene tartrate[2]	Estrogen receptor (ER)	III
	Axitinib	Vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)	II
	Irinotecan hydrochloride[1,2]	DNA topoisomerase I	II
	Sunitinib malate[2]	Vascular endothelial growth factor receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), platelet-derived growth factor receptor β (PDGFRβ)/Flt-3 (Flk-2/Stk1)	II

Continuation

Treatment of Breast Cancer by Source

Source	Condition	Drug	Phase
Pfizer	PD-325901	Mitogen-activated protein/extracellular signal-related protein kinase (MEK)	I/II
PharmaMar	Trabectedin[2]		II
Pharmexa	PX-104.1	HER2/neu/erbB2	II
Provectus	PV-10		I
Roche	Bevacizumab[1,2]	Vascular endothelial growth factor (VEGF)	Prereg.
	KOS-862 (R-1492)	Tubulin	II
	Pertuzumab	HER2/neu/erbB2	II
	R-1550	MUC1 (CD227 antigen)	I
Sanofi-Aventis	Larotaxel dihydrate	Tubulin	II/III
	XRP-6258	Tubulin	II
Schering	AG Tocosol™ Paclitaxel[2]	Tubulin	III
Schering AG (Berlex)	ZK-EPO	Tubulin	II
Schering-Plough	Lonafarnib[2]	Farnesyltransferase	II
Serono	Adecatumumab	Epithelial cell adhesion molecule (Ep-CAM)	II
Sonus	Tocosol™ Paclitaxel[2]	Tubulin	III
Taiho	TAS-108	Estrogen receptor (ER)	II (US)
	TSU-68	Vascular endothelial growth factor receptor-2 (VEGFR-2; Flk-1/KDR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR)	II
	TAS-108		I (JP)
Tapestry Pharmaceuticals	TPI-287	Tubulin	I
Trion Pharma	Ertumaxomab	HER2/neu/erbB2	II
University of Copenhagen	p53-DC Vaccine	p53	I/II
University of Texas System	Arsenic trioxide1		II
ViRexx	BrevaRex®	MUC1 (CD227 antigen)	I/II
Wyeth	Temsirolimus[2]	Mammalian target of rapamycin (mTOR)	Discontinued
Xanthus	Imidacrine dihydrochloride[2]	DNA topoisomerase II	II
YM BioSciences	Tesmilifene hydrochloride[2]	Estrogen receptor (ER), histamine receptor	III

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

Drugs Under Development for the Treatment of Breast Cancer

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Prous Science, P.O. Box 540, 08080 Barcelona, Spain

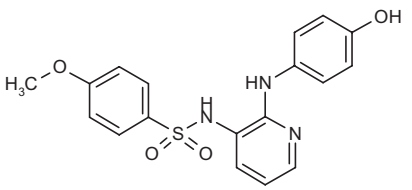
ABI-007

ABI-007 is a product comprised of paclitaxel protein-bound particles for injectable suspension, which was launched by the former American Pharmaceutical Partners, which subsequently merged with its parent company American BioScience to form Abraxis 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 metastatic melanoma. Additional phase II trials are ongoing at Abraxis for the treatment of head and neck cancer, and the company 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 BioScience 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 paclitaxel (Taxol®) in patients with advanced metastatic melanoma. ABI-007 is the first in a new class of protein-bound particle drugs prepared using 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.

ABIO-05/01

A cytotoxic cell line derived from the cells of a child with a rare form of T-cell leukemia, ABIO-05/01 is currently in phase I/II development for the treatment of peritoneal carcinosis at Abiogen. ABIO-05/01 is also being studied for the treatment of metastatic breast cancer and pediatric solid tumors. Preclinical data show that ABIO-05/01 cells are effective against a number of cancers, including leukemia, lymphoma, ovarian, prostate, breast and brain cancer. Safety has been demonstrated in preclinical studies using both nonirradiated and lethally irradiated ABIO-05/01 cells.

ABT-751



ABT-751, an antimitotic tubulin polymerization inhibitor discovered by Eisai, inhibits the assembly of microtubules, which play an essential role in cell division, migration and other functions that enable cancer to grow and spread. ABT-751 is currently in phase II development by licensee Abbott for the once-daily oral treatment of colorectal and kidney cancer, NSCLC and paclitaxel-refractory breast cancer. The NCI is conducting a phase II trial of ABT-751 in paclitaxel-refractory NSCLC. Phase I trials are under way at the M.D. Anderson Cancer Center and the NCI for the treatment of hematological malignancies and for the treatment of pediatric patients with refractory

solid tumors. In July 2000, Eisai and Abbott signed a licensing agreement granting Abbott worldwide development and marketing rights to ABT-751, except in Japan and Asia, where Eisai retains exclusive rights.

ActiVin®

ActiVin® is an all-natural grape seed extract rich in proanthocyanidin, an antioxidant known to protect cells from lipid peroxidation, inhibit tumor cell growth and inhibit enzymes involved in HIV replication. The product is marketed by Dry Creek Nutrition for use as a nutritional supplement. The NCI is conducting early clinical trials to evaluate the potential of ActiVin® for the prevention of breast cancer in high-risk, healthy postmenopausal women. In preclinical studies, grape seed proanthocyanidins were significantly more active than vitamin E or vitamin C in scavenging superoxide anions and hydroxyl radicals *in vitro*. The product was originally developed by InterHealth Nutraceuticals and was later acquired by Dry Creek Nutrition.

Adecatumumab

Phase II clinical testing is under way for adecatumumab, a fully humanized, monoclonal pan-carcinoma antibody directed against the epithelial cell adhesion molecule (Ep-CAM), for the treatment of hormone-refractory prostate cancer and metastatic breast cancer. Adecatumumab, discovered by Micromet, may enhance the antitumor activity of chemotherapeutic agents, as it has the potential to eliminate cancer cells that are momentarily dormant. Micromet developed adecatumumab based on Cambridge Antibody Technology's antibody phage display technology. In 2004, Micromet and Serono signed an exclusive collaboration and license agreement for the worldwide development and commercialization of the antibody. Pursuant to the agreement, Serono will begin clinical development of adecatumumab following completion of the ongoing phase II clinical trials by Micromet. Boehringer Ingelheim is responsible for the manufacture of the drug candidate.

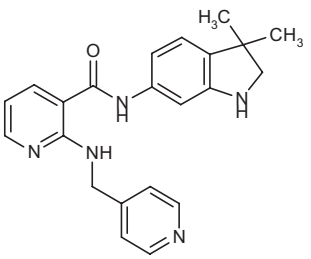
Advexin®

Ad5CMV-p53, also known as Advexin® gene therapy, is in phase III development at Introgen for the treatment of squamous cell carcinoma of the head and neck. The trials are evaluating both Advexin® monotherapy and Advexin® in combination with two other standard chemotherapies, cisplatin and 5-fluorouracil. The company has completed phase II trials with Advexin® for the treatment of NSCLC and breast cancer. Phase II trials are also under way at Introgen for the treatment of esophagel cancer. 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® induces the expression of the tumor suppressor p53 protein in very high concentrations 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 design 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.

AE-37

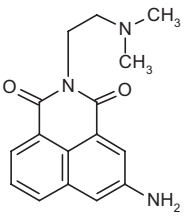
Antigen Express is conducting early clinical trials with AE-37, a cancer vaccine, for the treatment of *HER2/neu*-positive breast cancer patients. The compound is a second-generation peptide vaccine designed to stimulate a potent and specific immune response against tumors expressing the *HER2/neu* oncogene. A significant percentage of breast cancers, as well as cancers of the lung, colon, stomach and pancreas, express this oncogene. A strong immune response against *HER2/neu* offers the potential to kill tumor cells that have spread to parts of the body distant from the primary tumor.

AMG-706



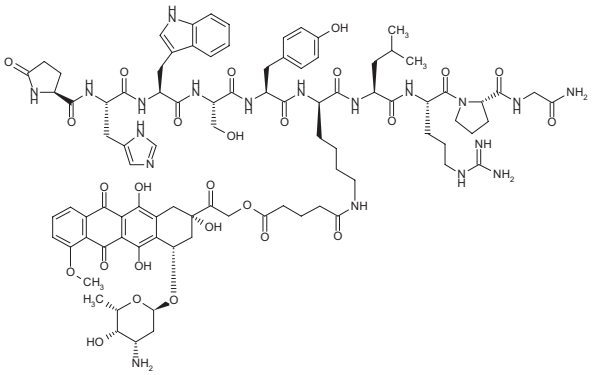
AMG-706, an oral multitargeted kinase inhibitor that works by selectively targeting all known vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), Kit and Ret receptors, is currently being evaluated in phase II clinical trials for the treatment of imatinib-resistant gastrointestinal stromal tumors (GISTs). Developed at Amgen, the compound is also being evaluated as both monotherapy and in combination with other agents in the treatment of bladder, breast, colorectal, lung, thyroid and ovarian cancers. The FDA awarded fast track status to AMG-706 in 2004.

Amonafide



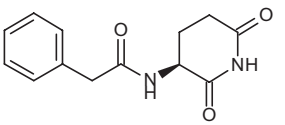
The second-generation topoisomerase inhibitor and intercalating agent amonafide (Quinamed®) is currently in phase II development at ChemGenex for the treatment of prostate cancer refractory to chemotherapy, breast and ovarian cancers. Xanthus is evaluating a new salt form of amonafide (amonafide L-malate) in combination with cytosine arabinoside (araC) in phase II clinical trials for the treatment of secondary acute myeloid leukemia (AML).

AN-152



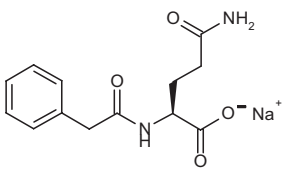
AN-152 is a cytotoxic analogue of luteinizing hormone-releasing hormone (LHRH) in which doxorubicin is linked to [D-Lys^6]-LHRH. The compound is currently in early clinical trials at AEterna Zentaris for the treatment of LHRH receptor-positive breast, endometrial and ovarian cancer. Receptors for LHRH have been found on a variety of cancers, including breast, prostate, ovarian and endometrial cancers. The drug candidate's mechanism of action, in addition to its relatively benign toxicity profile, makes it an attractive candidate for cancer therapy. AEterna Zentaris licensed AN-152 from Tulane University.

Antineoplaston A10

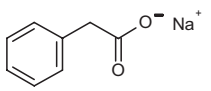


Antineoplaston A10 is a combination of naturally occurring medium- and small-sized peptides and amino acid derivatives isolated from healthy human blood and urine that interrupts the activity of the *RAS* oncogene and stimulates *p53* tumor suppressor genes, while not affecting healthy cells. The Burzynski Research Institute (BRI) is evaluating the agent in phase II trials for several indications, including brain stem glioma in children and adults, primary central nervous system lymphoma, residual or recurrent anaplastic astrocytoma, low-grade astrocytoma in children, adenocarcinoma of the colon, stage IV lung cancer, stage IV pancreatic cancer, ependymoma in children and adult patients, low-grade non-Hodgkin's lymphoma (NHL), stage IV melanoma, multiple myeloma, metastatic or incurable Merkel cell carcinoma, adrenocortical carcinoma, esophageal cancer, NSCLC, malignant mesothelioma, oligodendroglioma in adult patients and adenocarcinoma of unknown origin. BRI is also evaluating antineoplaston A10 in combination with methotrexate in patients with stage IV or recurrent breast cancer and in combination with total androgen blockade for the treatment of stage III/IV or recurrent prostate cancer. In 2004, the FDA granted orphan drug designation to antineoplaston A10 for the treatment of brain stem glioma.

Antineoplaston AS2-1



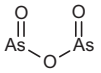
Antineoplaston AS2-5



Sodium phenylacetate

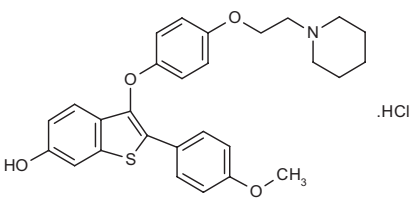
BRI is also evaluating antineoplaston AS2-1 (a combination of antineoplaston AS2-5 and sodium phenylacetate), a metabolite of antineoplaston A10 that inhibits the incorporation of glutamine into proteins in cancer cells, in phase II trials for the treatment of brain stem glioma, recurrent or refractory high-grade glioma, stage IV or recurrent breast cancer, stage IV lung cancer, metastatic or incurable Merkel cell carcinoma, astrocytoma in adults and children, and brain cancer. BRI is also conducting phase II trials of antineoplaston AS2-1 in combination with antineoplaston A10 in patients with recurrent adenocarcinoma of the colon and esophagus. The NCI is investigating antineoplaston AS2-1 in phase II trials for the treatment of colorectal cancer. In 2004, the FDA assigned orphan drug designation to antineoplaston AS2-1 for the treatment of brain stem glioma.

Arsenic Trioxide



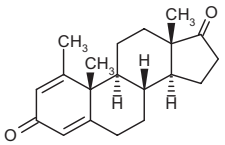
Arsenic trioxide is a pharmaceutical-grade arsenic compound launched in the U.S. in 2000 by Cell Therapeutics as Trisenox® for the treatment of relapsed or refractory acute promyelocytic leukemia (APL). In 2002 and 2004, marketing authorization was granted in the E.U. and Japan, respectively, for APL, and although the product was subsequently launched in several European countries, market launch in Japan is pending. Arsenic trioxide, developed by the Shanghai Second Medical University, appears to have multiple targets and mechanisms of antileukemic activity. The drug degrades PML/RAR-α, a protein that causes abnormal levels of immature white blood cells while simultaneously forcing immature cancer cells to self-destruct via apoptosis. Arsenic trioxide has been shown to induce apoptosis by producing reactive oxygen species and mitochondrial damage *in vitro* and to activate caspase *in vitro* and in humans. Furthermore, downregulation of VEGF production by tumor cells has been shown to stimulate apoptosis of tumor-supporting endothelial cells. More than 70 clinical trials of arsenic trioxide as monotherapy or in combination with other therapies are planned or ongoing. Cephalon and the NCI are evaluating arsenic trioxide in early clinical trials for recurrent malignant glioma, and the NCI is conducting additional trials for several indications, including stomach and esophageal cancer, astrocytoma and glioblastoma multiforme. The University of Texas System is studying the compound in phase II trials for the treatment of breast cancer and NSCLC. In 2000, Cell Therapeutics acquired the proprietary rights to arsenic trioxide for leukemia and other cancers, and in 2005 the company granted worldwide marketing, sales and development rights to the product to Cephalon. Arsenic trioxide has been granted orphan drug status for several indications in the U.S., including the treatment of APL, multiple myeloma, myelodysplastic syndromes, CML, chronic lymphocytic leukemia (CLL), AML and liver cancer. Orphan drug designation has also been received in the E.U. for the treatment of APL, multiple myeloma and myelodysplastic syndromes.

Arzoxifene Hydrochloride



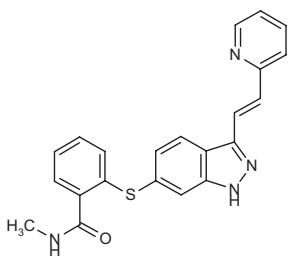
A third-generation selective estrogen receptor modulator (SERM), arzoxifene hydrochloride is in phase III clinical trials at Lilly for the treatment and prevention of osteoporosis and for the prevention of breast cancer in high-risk women. In early clinical trials, the drug demonstrated consistent reductions in free testosterone, dehydroepiandrosterone (DHEA), follicle-stimulating hormone (FSH), insulin-like growth factor-I (IGF-I) and its major binding protein (IGFBP-3) and osteocalcin, indicating positive effects on both breast cancer markers and bone turnover.

Atamestane



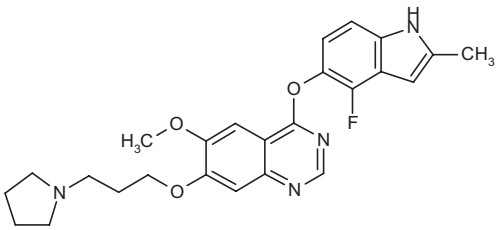
Atamestane is an orally bioavailable steroidal aromatase inhibitor in phase III clinical trials at Intarcia in combination with toremifene for preventing disease progression in postmenopausal women with advanced hormone-dependent breast cancer. Atamestane blocks the formation of estrogens from androgenic precursors in the body via the aromatase enzyme. Toremifene blocks circulating and intracellular estrogens from stimulating estrogen receptors in breast cancer cells. The combination of estrogen receptor blockade with toremifene and aromatase inhibition with atamestane addresses both key mechanisms by which estrogen drives breast cancer cell growth. Without this combined approach, estrogen receptor blockers, when used alone, lose effectiveness due to the development of tumor cell hypersensitivity to estrogens, making breast cancer cells sensitive to even the smallest amounts of estrogen. Aromatase inhibitors, when used alone, reduce the production of estrogen, but they do not reduce estrogen fat stores or dietary estrogen intake. Atamestane was originally developed at Schering AG and subsequently licensed to Intarcia.

Axitinib



Axitinib is an angiogenesis inhibitor in phase II clinical trials at Pfizer for the treatment of breast cancer and renal cell carcinoma. The drug is a potent, selective, orally active, small-molecule VEGF/PDGF receptor tyrosine kinase inhibitor. In preclinical trials, axitinib inhibited VEGF-stimulated proliferation and the survival of human umbilical vein endothelial cells (HUVEC), whereas it had no effect against basic fibroblast growth factor (bFGF)-stimulated responses, and it was also able to block VEGF-stimulated HUVEC adhesion to vitronectin.

AZD-2171

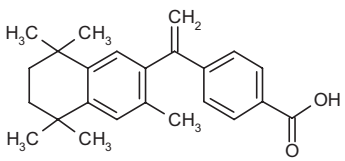


A highly potent inhibitor of VEGF receptor tyrosine kinases developed by AstraZeneca, AZD-2171 is currently undergoing phase II trials at the NCI for the treatment of breast, liver and ovarian cancers, as well as glioblastoma multiforme, melanoma and malignant mesothelioma. Early clinical trials are also under way at AstraZeneca for head and neck cancer and solid tumors. The National Cancer Institute of Canada is conducting early clinical studies for the treatment of colorectal cancer and NSCLC.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody targeting VEGF that was launched in the U.S. in 2004 as Avastin™ by Genentech for the first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-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 progression of metastatic disease. Bevacizumab also promotes the effective delivery of chemotherapy within the tumor. In January 2005, partner Roche received EMEA approval for this indication, and the product is now available in several E.U. countries, including Switzerland, Germany and the U.K. Approval has also been granted in Canada. At present, the companies are seeking approval for the indications of relapsed metastatic colorectal cancer, the treatment of advanced NSCLC in combination with platinum-based chemotherapy and the first-line treatment of metastatic breast cancer. Roche is conducting phase III trials as first-line therapy in combination with Xelox (oxaliplatin/capecitabine) or Folfox (5-fluorouracil/leucovorin) and as adjuvant therapy for this indication. Genentech is studying the drug in combination with Folfox as second-line treatment for metastatic colorectal cancer. Several phase III trials of the drug, including in combination with gemcitabine in patients with previously untreated advanced pancreatic cancer and in combination with interferon alfa-2b in patients with advanced renal cell carcinoma, are under way. Phase III trials are under way at Genentech and Roche for the treatment of kidney cancer. Furthermore, bevacizumab as monotherapy is in phase III clinical development for the treatment of prostate cancer and platinum-refractory ovarian cancer. Genentech is also conducting a phase II/III trial with or without chemotherapy in patients with advanced, metastatic or recurrent non-squamous cell NSCLC. Phase II trials are also under way at the company to evaluate the efficacy and safety of bevacizumab in combination with docetaxel or erlotinib for the treatment of advanced-stage NSCLC and in combination with chemotherapy for the treatment of bladder cancer. The NCI, which co-discovered bevacizumab with Genentech, is evaluating bevacizumab as monotherapy or in combination with other chemotherapeutic agents in phase II trials for the treatment of liver, breast, ovarian, stomach and head and neck cancer, malignant mesothelioma and Kaposi's sarcoma. The NCI is also conducting a phase I trial for the treatment of solid tumors in combination with sorafenib in patients with refractory, metastatic or unresectable disease.

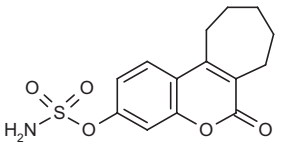
Bexarotene



Bexarotene is a retinoid X receptor (RXR) agonist launched by Ligand in 2000 in the U.S. as Targretin® capsules and gel for the treatment of cutaneous T-cell lymphoma (CTCL). European approval followed in March 2001 and the product is marketed in many major European countries, including Germany, the U.K. and France. Bexarotene activates the RXR receptors which function as transcription factors that regulate the expression of genes controlling cellular differentiation and proliferation. In March 2005, Ligand discontinued phase III trials of bexarotene capsules for the indication of NSCLC as first-line treatment in combination with other chemotherapeutic agents because the compound did not meet its endpoints of improved overall survival and projected 2-year survival. However, phase II trials of bexarotene as oral third-line monotherapy for NSCLC and second-line combination therapy for NSCLC are under way at the company. Additional phase II trials are being conducted with bexarotene gel for the treatment of hand dermatitis, psoriasis and alopecia areata. A capsule formulation is also in phase II trials at Ligand for the treatment of psoriasis. The NCI is evaluating bexarotene in phase II clinical trials as prophylaxis in women with a genetic risk of developing breast cancer. Ligand holds worldwide rights to market bexarotene capsules and will market the drug in the U.S., Canada and selected European markets. In Germany, France, the U.K. and other countries in northern Europe, Elan is responsible for marketing and distribution. Ligand has agreements with Ferrer for Spain, Portugal, Greece and Central and South America, and with Alfa Wassermann for Italy, for the marketing and distribution of bexarotene. In 1999, bexarotene was granted orphan drug designation by the FDA for the treatment of

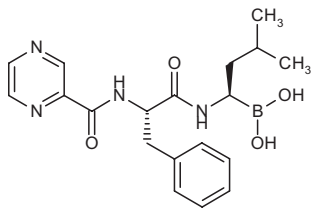
cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy.

BN-83495



The steroid (steryl) sulfatase (STS) inhibitor BN-83495 (formerly STX-64) is in early clinical trials at Ipsen for the treatment of postmenopausal breast cancer expressing estrogenic receptors. Evidence from preclinical trials suggests that BN-83495 is sequestered in red blood cells and that this interaction protects the drug from hydrolytic degradation in plasma. BN-83495 joined Ipsen's pipeline upon the company's acquisition of Sterix, a spin-off from the Imperial College of Science, Technology and Medicine in London and the University of Bath, originators of the compound.

Bortezomib



Millennium launched bortezomib, a potent and selective proteasome inhibitor, in the U.S. in 2003 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, therefore 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, B-cell lymphoma, mantle cell lymphoma and Waldenstrom'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, CLL, CML, Hodgkin's and non-Hodgkin's lymphoma and myelodysplasia. Millennium, in collaboration with Johnson & Johnson, is conducting phase II trials for both NSCLC and metastatic NSCLC. Early clinical studies are also under way for anaplastic astrocytoma, colorectal cancer and oligodendroglioma. Furthermore, Millennium is studying bortezomib for its potential in 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 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 the 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 holds marketing rights to the drug. Also under the agreement, Millennium, Ortho Biotech and Johnson & Johnson Pharmaceutical Research & 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.

BrevaRex®

BrevaRex® (AR20.5) is a murine monoclonal antibody specific for a particular soluble and tumor-cell bound form of MUC1 that is preferentially expressed by multiple myeloma and other cancer cells. AltaRex developed BrevaRex® to phase I/II clinical studies for the treatment of breast, lung and ovarian cancer and multiple myeloma. In December 2004, ViRexx acquired all issued and outstanding shares of AltaRex to form a new immunotherapy and embolotherapy company focused on ovarian and liver cancer, uterine fibroids and hepatitis B and C. The company plans to develop BrevaRex® for the treatment of breast cancer and multiple myeloma.

BZL-101

An apoptosis inducer, BZL-101 (Ban zhi lian) is in phase I/II clinical trials at Bionovo for the oral treatment of breast and ovarian cancer. The drug, an herbal extract from the *Scutellaria barbata* plant, induces apoptosis through mitochondrial transmembrane potentiation. Specifically, it translocates the apoptosis-inducing factor -1 (AIF-1) protein into the nucleus of the cell, causes chromatin condensation and DNA degradation and leads to cell death.

CEA-TRICOM

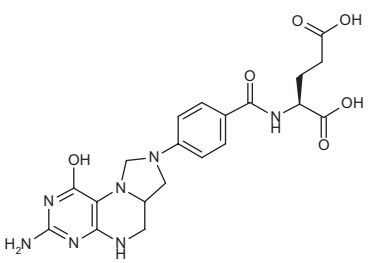
CEA-TRICOM, a recombinant, poxvirus-based vaccine that incorporates a triple dose of co-stimulatory molecules and carcinoembryonic antigen (CEA), is being evaluated at the NCI in phase II clinical trials for the treat-

ment of metastatic colorectal cancer. CEA-TRICOM is designed to stimulate and strengthen the body's immune system to kill colorectal cancer cells. The compound is also being studied by the NCI in early clinical trials for the treatment of breast and liver tumors.

Cetuximab

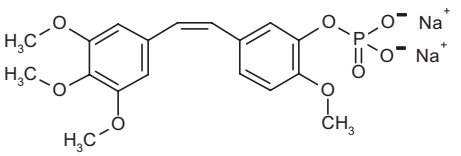
Cetuximab is a chimeric monoclonal antibody (MAb) originally developed by ImClone and first launched in Switzerland in 2003 as Erbitux™ by Merck KGaA as monotherapy and in combination with irinotecan for the treatment of irinotecan-refractory metastatic colorectal cancer. In 2006, the product was commercialized in Switzerland for an additional indication: the treatment, alone or in combination with high-dose radiation, of advanced squamous cell cancer of the head and neck. Approval for these indications has also been obtained in the E.U., where it is available in several countries, and many non-E.U. countries, and the product is available in the U.S. from Bristol-Myers Squibb. Cetuximab is in advanced clinical development for several indications, including the first-line treatment of colorectal cancer, recurrent or progressive NSCLC, unresectable or metastatic adenocarcinoma of the pancreas, head and neck and stomach cancer. In addition, phase II trials of cetuximab are ongoing for the treatment of cervical carcinoma, unresectable or metastatic esophageal and gastric cancer, unresectable or metastatic hepatocellular carcinoma, metastatic colorectal, ovarian and breast cancer, among others. 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 therefore prevents signal transduction and tyrosine kinase autophosphorylation and, in turn, results in inhibition of cell growth, induction of apoptosis and decreased matrix metalloproteinase and vascular endothelial growth factor production. In 1998, Merck licensed from ImClone 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 Systems and Bristol-Myers Squibb established an agreement to co-develop and co-promote cetuximab in the U.S., Canada and Japan.

CoFactor™



A folate-based biomodulator developed to enhance the activity of 5-fluorouracil (5-FU) cancer therapy, CoFactor™ is being evaluated in phase II clinical trials by Adventrx for the treatment of metastatic colorectal cancer. It is also being studied in phase I/II trials for pancreatic, gastric and breast cancers. Originally developed by researchers at the University of Southern California and Sahlgrenska University Hospital, Sweden, CoFactor™ received orphan drug status from the FDA and the EMEA for the treatment of pancreatic cancer in 2004. Based upon previous data from clinical trials, CoFactor™ may greatly improve the quality of life of patients due to reduced doses of 5-FU and a reduced need for other chemotherapeutic agents.

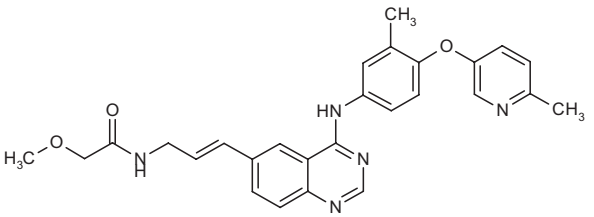
Combretastatin A-4 Phosphate



Clinical development of combretastatin A-4 phosphate (CA4P), a phosphate prodrug of the vascular targeting agent combretastatin A4, is under way at 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 rapidly converts to the active compound in the bloodstream, enters 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. In phase II trials, OxiGene is studying CA4P 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 studies 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 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

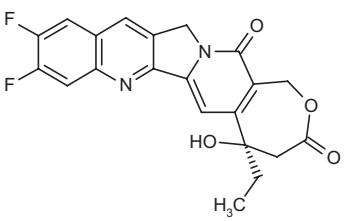
monotherapy for cervical cancer and in combination with carboplatin and paclitaxel for the treatment of solid tumors. Preclinical studies are under way at the company with CA4P in combination with bevacizumab for the treatment of colorectal cancer. In 2003, CA4P was granted orphan drug designation by the FDA for the treatment of anaplastic thyroid, medullary thyroid and stage IV papillary or follicular thyroid cancer.

CP-724714



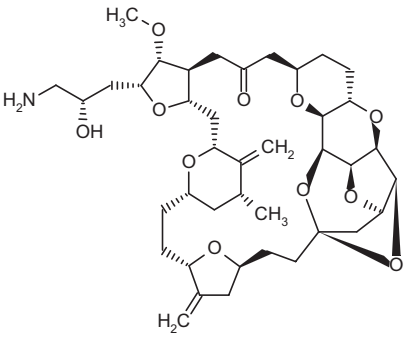
CP-724714 is a selective oral inhibitor of HER2 that is in early clinical trials at OSI Pharmaceuticals for the treatment of metastatic breast cancer. The *HER2* oncogene, when functioning normally, has been found to be a key component in regulating cell growth. The gene's overexpression has been demonstrated to correlate with aggressive cancer growth, particularly in metastatic breast cancer. Unlike a monoclonal antibody, which targets the extracellular domain of HER2, CP-724714 targets the intracellular tyrosine kinase activity. CP-724714 was jointly discovered through a collaboration formed in 1988 between OSI and Pfizer.

Diflomotecan



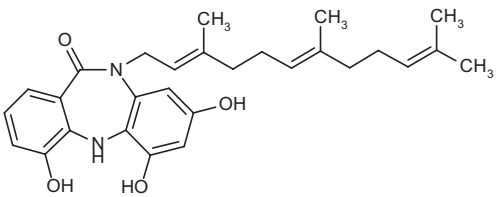
Diflomotecan (BN-80915) is a DNA topoisomerase I inhibitor with improved safety and efficacy that is currently in phase II evaluation by Ipsen for several metastatic solid cancers, including breast, colorectal and prostate cancer. The drug acts by blocking a key enzyme in the DNA transcription process, thereby inhibiting the proliferation of cancer cells. During phase I clinical trials, diflomotecan demonstrated high oral bioavailability, a potentially broad spectrum of antiproliferative activity, low gastrointestinal toxicity and no cumulative hemotoxicity.

E-7389



The halichondrin B analogue E-7389 is being tested in phase II clinical trials at Eisai for the treatment of advanced or metastatic breast cancer previously treated with chemotherapy and for the treatment of advanced NSCLC progressing after platinum-based chemotherapy. Early clinical trials are also under way for the treatment of prostate cancer. Halichondrin B, a structurally complex marine product, is a highly potent cytotoxic and antitumor agent. Limited supplies of the natural product led Eisai researchers to synthesize and evaluate structurally simpler analogues. E-7389 is a result of this research, demonstrating cell cycle block in the G2/M phase, disruption of mitotic spindles and inhibition of tubulin polymerization, a mechanism of action identical to that of the parent compound.

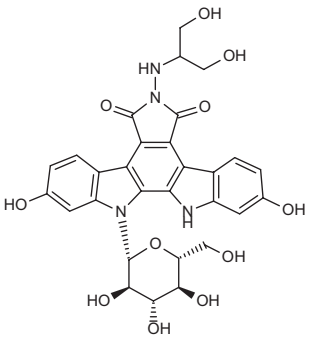
ECO-04601



Ecopia's ECO-04601 is a structurally novel farnesylated dibenzodiazepinone in preclinical studies for the treatment of leukemia and melanoma. In early 2006, Ecopia received a no objection letter from the Therapeutic Products Directorate of Health Canada with respect to filed INDs and the company expects to commence phase I clinical testing for the treatment of patients with glioblastoma, breast, prostate, ovarian, lung or colon cancer who are refractory to current chemotherapies. Derived from microorganisms that live in common soil, ECO-04601 was discovered using Ecopia's DECIPHER® technology, which uses a combination of genomics and bioinformatics to make computer predictions of the chemical structure of potential new drugs based on gene sequence information obtained by scanning the actinomycetes genome. The compound crosses the blood-brain barrier and is effective in significantly inhibiting the growth of primary brain tumors, as well as other types of cancer. ECO-04601 has been shown to increase the expression

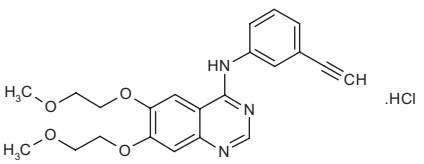
of several genes involved in the regulation of apoptosis and signal transduction, including mitochondrial peripheral benzodiazepine receptor (PBR) mRNA. The PBR is a critical component of the mitochondrial permeability transition pore (MPTP). This multiprotein complex is located at the contact site between inner and outer mitochondrial membranes, and is involved in the initiation and regulation of apoptosis.

Edotecarin



Edotecarin is an antimitotic agent in phase II clinical trials at the NCI for the treatment of anthracycline- and taxane-refractory or chemoresistant locally advanced or metastatic breast cancer. Banyu and the NCI are also evaluating the drug candidate in phase I trials for the treatment of solid tumors. Edotecarin inhibits mitotic events in tumor cells through DNA intercalation and inhibition of DNA topoisomerase I. Originally developed at Banyu and Merck & Co., the drug was subsequently licensed to Pfizer, where it was studied for the treatment of breast and stomach cancer. Development rights were later returned to Banyu when trials at Pfizer were terminated due to insufficient activity against those cancer types.

Erlotinib Hydrochloride

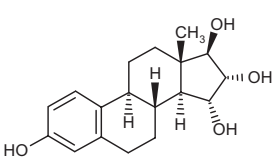


An epidermal growth factor receptor (EGFR, erbB1) inhibitor, erlotinib hydrochloride was launched by Genentech, OSI Pharmaceuticals and Roche in the U.S. in 2004 as Tarceva® for the oral treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In September 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 the HER1/EGFR receptor, thereby blocking the HER1/EGFR signaling pathway inside the cell. Phase III 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 is evaluating the potential of the drug in phase III trials for head and neck cancer. The companies, as well as 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 and stomach cancer, glioma, sarcoma and esophageal cancer. 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 in progress. 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 and pediatric brain cancer and solid tumors. Originally discovered by Pfizer, erlotinib is being developed under an alliance established by OSI with Genentech and Roche.

Ertumaxomab

Ertumaxomab is a trifunctional bispecific monoclonal antibody in phase II clinical trials at Trion Pharma for the treatment of breast cancer. Trifunctional bispecific monoclonal antibodies are a new class of chimeric antibodies that induce tumor cell lysis through simultaneous binding to proteins expressed on the cell surface of tumor cells, T-cells and accessory cells such as macrophages and dendritic cells. Ertumaxomab is an anti-HER2/neu and CD3 antibody, which also binds to Fcγ receptors I and III via its intact Fc region. The drug candidate, originally designed at Trion Pharma, has been in development in collaboration with Fresenius since 2001.

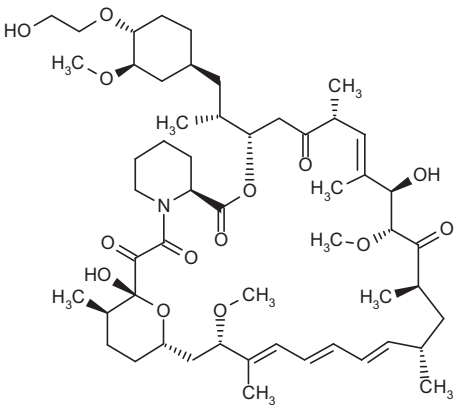
Estetrol



Estetrol is a SERM in phase I/II clinical trials at Pantarhei Bioscience for the treatment of breast cancer, osteoporosis and postmenopausal syndrome and for the

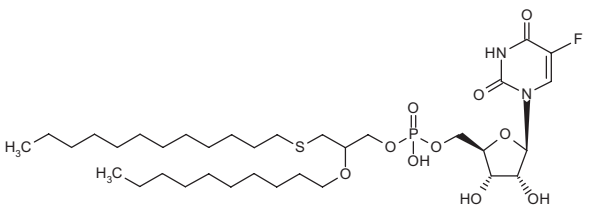
prevention of pregnancy. When administered orally, estetrol, a natural human estrogen which is solely produced in large quantities during human pregnancy by the male and female fetal liver, acts as an estrogen agonist on the vagina, uterus and bone. It has been shown to suppress hot flushes and inhibit ovulation. Furthermore, the finding that estetrol dose-dependently prevented the development of breast tumors and inhibited pre-existing breast tumors in the DMBA rat model suggests that it also acts as an estrogen antagonist for the breast.

Everolimus



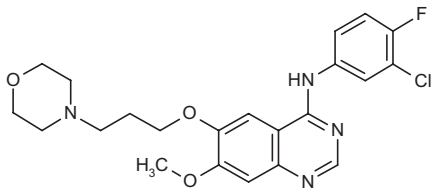
A novel proliferation signal inhibitor with immunosuppressive and antiproliferative properties, everolimus was initially launched by Novartis in 2004 for the prevention of rejection episodes following heart or kidney transplantation in combination with ciclosporin. It is presently being evaluated in extensive clinical trials for several oncological indications, including the treatment of endometrial, neuroendocrine and breast cancer and other solid tumors, as well as hematological cancers, in collaboration with the NCI, the M.D. Anderson Cancer Center and the Memorial Sloan-Kettering Cancer Center. Novartis is also conducting early clinical trials with everolimus for the treatment of tuberous sclerosis.

Fosfluridine Tidoxil



Fosfluridine tidoxil is a once-daily oral antitumor agent derived by applying Heidelberg Pharma's Enhanced ProDrug Technology to 5-fluorouridine, a metabolite of the widely used anticancer antimetabolite 5-fluorouracil (5-FU). The drug candidate is currently in phase II clinical development for the treatment of colorectal and breast cancer and actinic keratosis. In contrast to prodrugs of 5-FU such as capecitabine, the intracellular activation of fosfluridine to its active metabolite 5-fluorouridine monophosphate is a one-step reaction through the activity of a distinct cleaving enzyme. Results from preclinical studies indicate that fosfluridine is not distributed to the bone marrow, results which have been confirmed by clinical observations of a lack of bone marrow toxicity.

Gefitinib

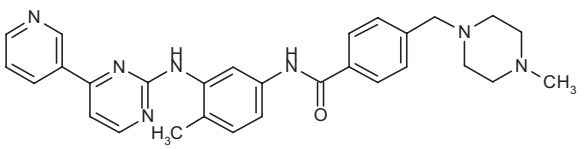


Gefitinib (ZD-1839), an EGFR (erbB1) inhibitor that blocks the signal transduction pathways induced by EGFR, was first launched in 2002 in Japan as Iressa™ tablets for the treatment of NSCLC. The drug was the first in a new class of anticancer drugs known as EGFR tyrosine kinase inhibitors to gain market approval and is currently available in a number of other countries around the world, including the U.S., 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 this, 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 breast 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 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 being conducted at the NCI in children with brain stem gliomas. Early clinical trials of gefitinib as monotherapy for the treatment of pediatric solid tumors are also ongoing at the NCI. Phase II trials are being conducted at the EORTC for the treatment of metastatic breast cancer and synovial sarcoma and at the M.D. Anderson Cancer Center for the treatment of squamous cell carcinoma. 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.

GTI-2040

GTI-2040 is an antisense oligonucleotide that binds to the messenger RNA encoding the R2 component of ribonucleotide reductase, an enzyme essential for DNA synthesis and cell proliferation. The R2 component is elevated in many tumors and may also play a role in tumor progression as a signal molecule in a molecular pathway important in determining malignancy. At present, Lorus Therapeutics is evaluating the drug in combination with chemotherapy in phase II trials for the treatment of renal cell carcinoma. The nucleotide is also in phase II development pursuant to a research collaboration agreement signed in 2002 by Lorus and the NCI for several cancer indications. As a result of this collaboration, GTI-2040 in combination with chemotherapy is in phase II testing for the treatment of colon, breast and prostate cancer, NSCLC, solid tumors and AML. GTI-2040 has received orphan drug designation by the FDA for the treatment of renal cell carcinoma and AML.

Imatinib Mesilate



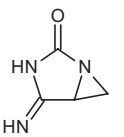
$.CH_3SO_3H$

Imatinib mesilate is a small-molecule tyrosine kinase inhibitor first launched in the U.S. in 2001 by Novartis for the treatment of patients with Philadelphia chromosome-positive (Ph+) CML in blast crisis, accelerated phase or 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 mesilate is approved for adult patients in all phases of Ph+ CML. 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 GISTs. Regulatory applications have been filed in the U.S., the E.U. and Japan seeking approval of the drug for the treatment of adult patients with Ph+ acute lymphoblastic leukemia (Ph+ ALL). In combination with chemotherapy, it is in phase I trials in patients with recurrent small cell lung cancer at the NCI and the NCI is also conducting phase I/II trials of the drug as monotherapy for the treatment of glioma and oligodendroglioma, and in combination with bevacizumab in patients with advanced melanoma. Phase II NCI trials are under way for colorectal, small cell lung, metastatic prostate, ovarian and skin cancer, lymphocytic leukemia, Ewing's sarcoma and HIV-related Kaposi's sarcoma, and alone or in combination for the treatment of breast cancer. In addition, a phase III trial is ongoing at the NCI with the drug as adjuvant therapy for GISTs. Novartis is conducting phase II trials with the product for leukemia, idiopathic pulmonary fibrosis and hormone-refractory prostate cancer. Phase III trials are also under way at the company as monotherapy for the treatment of astrocytoma and with high-dose imatinib mesilate for the treatment of CML, as a single agent for the treatment of blood cancer and in combination with hydroxyurea and/or temozolomide for the treatment of glioblastoma multiforme. Phase II trials are ongoing at the EORTC and the M.D. Anderson Cancer Center for glioma and lymphocytic leukemia, respectively. The Institut Gustave Rossy is conducting phase II trials in children, adolescents and young adults for the treatment of cancer, including head and neck cancer, while the NIH is studying the compound in phase II for the treatment of hypereosinophilic syndrome. An additional phase II trial in combination with docetaxel (Taxotere®) is under way at the University of Kansas Medical Center for the treatment of NSCLC. In 2001, imatinib mesilate 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 for 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.

IMC-18F1

The anti-VEGFR-1 (Flt-1) human monoclonal antibody IMC-18F1 is in early clinical development at ImClone for the treatment of breast and colorectal cancer. A high-affinity neutralizing antibody, IMC-18F1 specifically blocks VEGFR-1 activation and signaling in endothelial and VEGFR-1-expressing tumor cells. In preclinical studies, IMC-18F1 was shown to significantly suppress the growth of human breast tumors in several xenograft models.

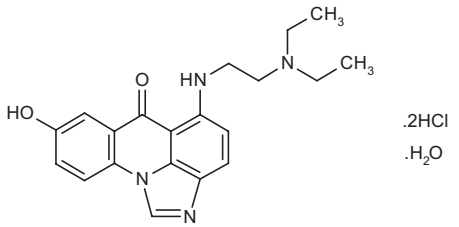
Imexon



Imexon is an apoptosis inducer in phase I/II trials at AmpliMed in combination with other chemotherapies for the treatment of breast, lung and prostate cancer, as well as previously untreated advanced pancreatic cancer and previously untreated unresectable stage III or IV malignant melanoma. Phase I trials are also under way at the company for use as monotherapy in the treatment of late-stage cancer. AmpliMed and Heidelber Pharma are evaluating the drug candidate in phase I/II trials for the treat-

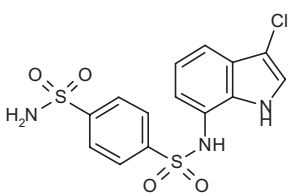
ment of multiple myeloma. Imexon is a small molecule belonging to the cyanoaziridine class of compounds. It has a unique mechanism of action in attacking cancer and appears to avoid bone marrow toxicity and drug resistance. It is thought to act by causing the disruption of mitochondria, resulting in the leakage of toxic substances that kill cancer cells. Other mechanisms involve the disruption of cell division by increasing the uptake of other anticancer drugs into the DNA of cancer cells, or directly targeting an enzyme involved in a critical pathway for DNA synthesis. Originally developed at Roche, imexon was assigned orphan drug designation in the U.S. for the treatment of melanoma, multiple myeloma, pancreatic and ovarian cancer, and in the E.U. for the treatment of pancreatic and ovarian cancer.

Imidacrine Dihydrochloride



An imidazoacridinone derivative with antitumor properties, imidacrine dihydrochloride is in phase II clinical trials at Xanthus for the intravenous treatment of metastatic breast cancer and metastatic colorectal cancer refractory to oxaliplatin and/or irinotecan. The drug is also undergoing early clinical trials at Xanthus for advanced solid tumors. Preclinical studies focusing on the treatment of multiple sclerosis are also under way at the company. Imidacrine has been shown to block the cell cycle at the G2 phase. Preclinical trials have revealed that following G2 arrest, tumor cells treated with imidacrine progress to mitosis but do not undergo cytokinesis and eventually die in a process that resembles abortive mitosis or mitotic catastrophe. The drug candidate is the result of deliberate chemical synthesis based on mitoxantrone, with the intent to maintain efficacy while reducing specific toxicities such as cardiotoxicity and hematotoxicity. Originally developed at the Politechnika Gdanska, imidacrine was subsequently licensed to BTG. In a later agreement, Xanthus licensed intellectual property related to the drug from BTG.

Indisulam



Eisai's novel sulfonamide apoptosis-inducing anticancer agent indisulam blocks cell cycle progression in the G1 phase. The drug is in phase II development as monotherapy for the treatment of gastrointestinal cancer, and in combination with irinotecan for the treatment of colorectal and small cell lung cancer. The company discontinued its development for breast cancer last year.

INGN-225

INGN-225 is a therapeutic vaccine using the patient's own dendritic cells previously stimulated with Introgen's Advexin® *p53* gene therapy. The vaccine is being evaluated by Introgen in phase I/II trials for the treatment of NSCLC and breast cancer. Advexin® supplies p53 protein in very high concentrations in cancer tissue and selectively kills cancer cells while not harming the surrounding normal cells.

INGN-241

INGN-241, an adenoviral vector carrying the *mda-7/IL-24* gene, has been shown to exhibit tumor-selective apoptosis, immunostimulating and antiangiogenic activity. Phase II clinical trials are under way at Introgen for the treatment of metastatic melanoma. The company is also studying the gene therapy in early clinical trials for the treatment of other cancer indications, including breast and colorectal cancer, NSCLC, solid tumors and lymphoma. Additional preclinical studies have evaluated the potential of the gene therapy alone or in combination with other therapies for the treatment of lung, ovarian and prostate cancers. INGN-241 was developed using Introgen's proprietary adenovector technology to deliver the gene encoding the mda-7 protein. The company holds an exclusive worldwide license for all gene therapy applications relating to the *mda-7* gene from Corixa. The *mda-7 gene*, the active component in INGN-241, was discovered by researchers at Columbia University.

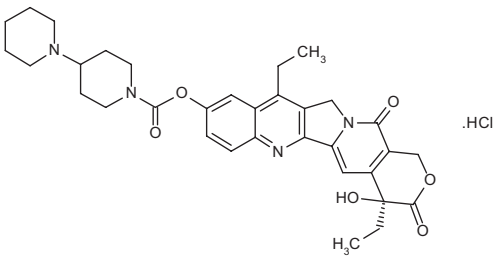
INX-0125

Inex has filed INDs with the FDA seeking approval to begin clinical evaluation of INX-0125 (sphingosomal vinorelbine), a *Vinca* alkaloid encapsulated in the liposomal Transmembrane Carrier System (TCS), for the treatment of breast, colorectal and lung cancers. In March 2006, Inex signed a letter of intent to license three products from its targeted chemotherapy pipeline to Hana Biosciences, including INX-0125. Upon closing of the agreement, Hana will be responsible for all future development and commercialization of INX-0125, including all future expenses. The antimitotic activity of vinorelbine is based on the compound's tubulin polymerization-inhibitory activity.

Ipilimumab

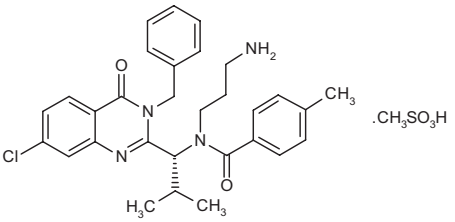
Ipilimumab (MDX-010), a fully human antibody targeting the CTLA-4 receptor, is currently in phase III development as monotherapy or in combination with other therapies for the treatment of metastatic melanoma. The drug candidate is also being evaluated in phase II trials in other oncology indications, including metastatic breast cancer, metastatic kidney cancer, synovial sarcoma, pancreatic cancer and as monotherapy or in combination with docetaxel for the treatment of prostate cancer. NCI-sponsored phase II trials are under way for the treatment of intraocular melanoma in combination with melanoma peptide vaccine in patients with stage III or IV disease, as well as for the treatment of lymphoma. In 2004, the compound received orphan drug designation from the FDA for the treatment of high-risk stage II, III and IV melanoma. Originally discovered at Medarex, ipilimumab is being developed in collaboration with Bristol-Myers Squibb.

Irinotecan Hydrochloride



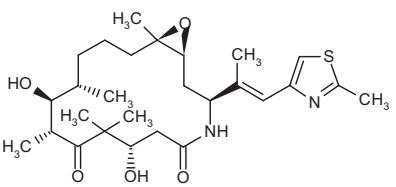
Originally developed by Yakult Honsha, irinotecan hydrochloride has been marketed for over 20 years by licensee Daiichi Pharmaceutical for the treatment of lung cancer and cancers of the uterine cervix and ovaries. The drug, a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*, is an antineoplastic agent from the topoisomerase I inhibitor class. In Europe, irinotecan was first approved in France in 1995 as second-line treatment for metastatic colorectal cancer after 5-fluorouracil 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. More recently, in 2004, Daiichi filed a regulatory application seeking approval to market irinotecan for the treatment of pancreatic cancer in Japan. At present, the compound is in phase III development at Aventis Pharma, another licensee, for the treatment of small cell lung 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, solid tumors and sarcoma. The NCI also has a phase I/II trial under way with irinotecan for the treatment of glioblastoma multiforme and a phase II trial of the drug in combination with other chemotherapeutic agents for the treatment of stomach cancer. Additional development is taking place at Pfizer, which is conducting phase II trials for the treatment of breast cancer, and the EORTC is evaluating its potential for the treatment of penile cancer. St. Jude's Research Hospital is conducting early clinical trials with irinotecan in combination with gefitinib (Iressa™; see above) for the treatment of glioblastoma multiforme and neuroblastoma.

Ispinesib Mesilate



Ispinesib mesilate (SB-715992) is a novel small-molecule oncology drug candidate directed against kinesin spindle protein (KSP), currently in phase II development by GlaxoSmithKline for the treatment of breast and ovarian cancer and NSCLC. The NCI is evaluating ispinesib in early clinical trials 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 also conducting phase II trials for the second-line treatment of patients with hormone-refractory prostate cancer and 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, via their novel mechanism of action, have the potential to exhibit an improved therapeutic profile over existing antimitotic drugs.

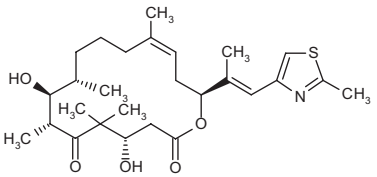
Ixabepilone



The novel semisynthetic epothilone analogue ixabepilone, developed by Bristol-Myers Squibb, is in clinical development for the treatment of certain cancers. The company is evaluating ixabepilone in combination with capecitabine in a phase III trial in patients with advanced

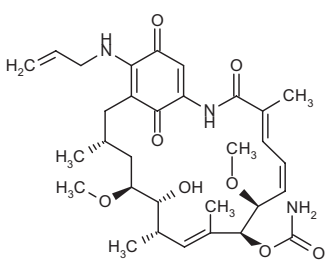
breast cancer previously treated with an anthracycline and a taxane. Ixabepilone is also the subject of numerous phase II trials under the direction of Bristol-Myers Squibb, including trials for the treatment of breast, kidney, pancreatic and prostate cancer. The NCI is conducting several phase II trials with ixabepilone as monotherapy for the treatment of kidney, germ cell ovarian, prostate, testicular, endometrial and gallbladder cancer, relapsed or refractory aggressive NHL, liver cancer and CLL, as well as in combination with other chemotherapeutic agents for the treatment of metastatic breast cancer. In addition, the NCI is evaluating ixabepilone in a phase I/II trial for the treatment of glioma and phase I trials for the treatment of lymphoma and solid tumors, including advanced small intestinal cancer. Like epothilone B, ixabepilone is a stabilizing tubulin antagonist with broad antitumor activity. Due to its distinct tubulin-binding mode, ixabepilone may be less susceptible to mechanisms of multiple drug resistance than taxanes.

KOS-862 (R-1492)



KOS-862 (R-1492, desoxyepothilone B), a polyketide that inhibits cancer cells by the same mechanism as paclitaxel, is currently in phase II development by Kosan Biosciences and licensee Roche for the treatment of metastatic breast cancer. Kosan is also studying KOS-862 in combination with carboplatin as a treatment for solid tumors. Preclinical models have shown the compound to be effective against paclitaxel-resistant tumors. Development for the treatment of colorectal cancer and NSCLC was discontinued; the trial in colorectal cancer was terminated due to unanticipated cumulative drug toxicities in patients who had been previously treated with oxaliplatin and the trial in NSCLC did not meet the primary objective of tumor response. KOS-862 and its backup compounds are being developed under a global development and commercialization agreement established by Roche and Kosan in 2002.

KOS-953



A proprietary formulation of 17-AAG, a heat shock protein 90 (Hsp90)-binding agent derived from polyketides, KOS-953 is being evaluated by Kosan Biosciences in phase II clinical trials for the treatment of stage III or IV metastatic melanoma in patients unresponsive to one prior regimen, as well as breast, ovarian, prostate and thyroid cancer and mantle cell lymphoma. The NCI is also conducting phase II trials for the treatment of kidney tumors in patients with Von Hippel-Lindau (VHL) disease, stage III and IV melanoma and metastatic breast cancer. Several early clinical trials with KOS-953 are under way at Kosan as monotherapy or in combination with bortezomib for the treatment of relapsed and refractory multiple myeloma. Additional phase I trials are ongoing at the NCI as monotherapy for the treatment of relapsed or refractory pediatric leukemia, NHL and advanced sarcoma, and in combination with chemotherapy for the treatment of solid tumors, CML, relapsed or refractory AML, ALL and myelodysplasia. 17-AAG inhibits Hsp90, a protein chaperone that binds to client proteins, subsequently disrupting the Hsp90-client protein complexes and leading to their degradation, and ultimately cell death. In 2002, Kosan and the NCI signed a CRADA for the clinical development of 17-AAG, and in 2004, 17-AAG received orphan drug designation from the FDA for the treatment of multiple myeloma and CML.

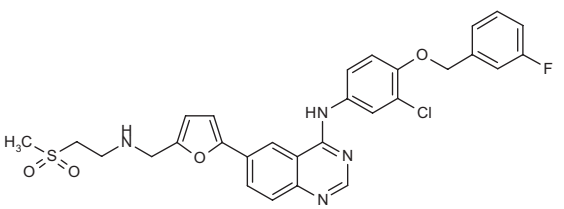
KU-59436

KU-59436 is an oral poly(ADP-ribose)polymerase (PARP, NAD+ ADP-ribosyltransferase) inhibitor in early clinical development at Kudos Pharmaceuticals, now a wholly owned subsidiary of AstraZeneca, for the treatment of breast cancer.

Labetuzumab

Phase I/II clinical trials are being conducted at Immunomedics with labetuzumab, a naked humanized antibody targeting CEA-expressing tumors, for the treatment of breast and colon cancer.

Lapatinib



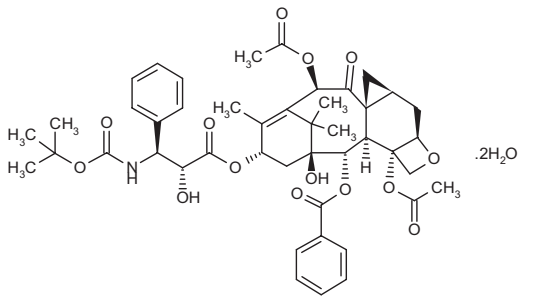
Lapatinib, a dual erbB1/erbB2 kinase inhibitor from GlaxoSmithKline, is currently undergoing phase III clinical trials for the oral treatment of metastatic breast, head and neck, lung, gastric, kidney and genitourinary cancer. The compound is also being evaluated for the treatment of brain, gallbladder, prostate, ovarian, endometrial and hepatobiliary 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.

Lapuleucel-T

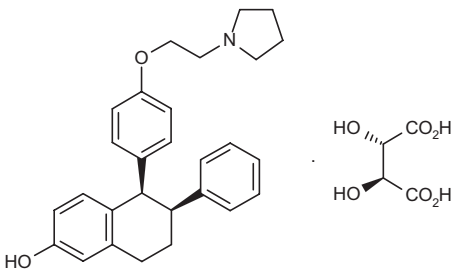
Dendreon's lapuleucel-T (APC-8024, Neuvenge) is a signal transduction pathway inhibitor in phase I trials at Dendreon for the treatment of breast, ovarian and colorectal cancers. The drug is an investigational immunotherapy targeting HER2/neu-positive cancers. HER2/neu is a growth factor receptor, the overexpression of which has been associated with a number of cancers, including breast, ovarian, colon and lung cancer. Dendreon's proprietary Antigen Delivery Cassette™ technology delivers small pieces of the HER2/neu protein to a patient's antigen-presenting cells (APCs). These specialized immune cells activate other cells of the immune system to seek out and destroy HER2/neu-containing cancer cells. Dendreon has agreements with Kirin Brewery and R.W. Johnson to develop its dendritic cell-based cancer therapies.

Larotaxel Dihydrate



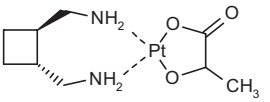
Larotaxel dihydrate (XRP-9881) is a taxoid tubulin inhibitor in phase II/III clinical trials at Sanofi-Aventis and the NCI for the treatment of refractory advanced or metastatic breast cancer.

Lasofoxifene Tartrate



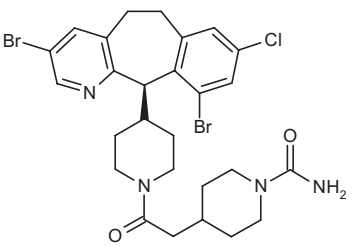
Lasofoxifene tartrate is a SERM licensed by Ligand to Pfizer for marketing and development. In 2004, Pfizer filed an NDA and an sNDA seeking FDA approval for the prevention of postmenopausal osteoporosis and for the treatment of atrophic vaginitis, respectively; however, in September 2005, the company received a nonapprovable letter for the former indication. An FDA decision regarding the atrophic vaginitis indication is still pending. In spite of the FDA decision's regarding postmenopausal osteoporosis, the drug candidate remains in phase III clinical development for this indication, as well as for the prevention of breast cancer. Like other members of the SERM class, lasofoxifene acts as an estrogen antagonist in breast and uterine tissues and as an estrogen agonist in bone and other tissues. The compound binds to estrogen receptors with comparable affinity to 17β-estradiol and in bone it duplicates many of the effects obtained following administration of estrogen.

Lobaplatin



A third-generation antineoplastic platinum derivative, lobaplatin is approved in China for the treatment of inoperable advanced breast cancer, small cell lung cancer and CML. Hainan Chang An holds marketing and manufacturing rights to lobaplatin in China, where the company is currently preparing market launch for the three approved indications. Originator AEterna Zentaris is currently evaluating the drug in phase II trials for all three indications. Lobaplatin has also demonstrated therapeutic activity in cancers of the head and neck and esophagus. Lobaplatin is available for partnerships worldwide, excluding China.

Lonafarnib



Lonafarnib, an apoptosis inducer and farnesyltransferase inhibitor, is in phase II clinical trials at Schering-Plough for the oral treatment of leukemia, breast cancer and other solid tumors. The drug is also in early clinical development for the treatment of head and neck cancer at the NCI and for the treatment of astrocytoma and oligodendroglioma at the EORTC. Schering-Plough discontinued a phase III clinical trial of lonafarnib for the treatment of NSCLC due to lack of sufficient evidence of efficacy from an interim data analysis; however, a phase III trial is under way at the company for the treatment of CML.

MetXia®

MetXia® is a gene-targeted prodrug activation compound comprised of a third-generation retroviral vector delivering the *CYP2B6* gene which encodes a cytochrome P-450 enzyme that activates cyclophosphamide to its active cytotoxic form. It is currently being evaluated in phase II clinical trials at Oxford BioMedica for the treatment of pancreatic cancer. It has also been studied in phase I/II trials for the treatment of breast cancer and melanoma. Oxford BioMedica licensed rights to the product from Massachusetts General Hospital, Boston University and Dana-Farber Cancer Institute in 1997. Oxford BioMedica is currently seeking commercial partners for co-development and marketing of MetXia®.

MKC-1

EntreMed is evaluating the antimitotic agent MKC-1 in phase II studies for the oral treatment of advanced and metastatic breast cancer and NSCLC. The drug candidate arrests cellular mitosis by inhibiting a novel intracellular target important in cellular trafficking that has been shown to be involved in cell division. Originally developed at Roche, MKC-1 was added to EntreMed's product pipeline in January 2006 upon the company's acquisition of Miikana Therapeutics.

Mycograb®

Mycograb® is a recombinant human monoclonal antibody that has been preregistered in the E.U. by NeuTec for the treatment of invasive candidiasis infections in combination with amphotericin B. The antibody is also undergoing phase I/II clinical trials in combination with docetaxel for the treatment of metastatic or recurrent breast cancer. Mycograb® binds to heat shock protein 90 (Hsp90), a tumor marker that appears on the outside of certain cancer cells and is needed for cancer cell survival. The antibody differs from all other Hsp90 inhibitors due to the fact that it was originally developed for the treatment of fungal infections. Mycograb® has a unique site of action that is not dependent on nucleotide displacement. The antibody was originally developed under a collaboration between NeuTec and the University of Manchester. In 2001, the EMEA designated Mycograb® an orphan drug for the treatment of invasive fungal infections, and in September 2002 the FDA followed suit, granting orphan drug designation for the treatment of invasive candidiasis.

OGX-111 (ISIS-112989)

OGX-011 (ISIS-112989), a second-generation antisense drug candidate designed to specifically inhibit the production of clusterin, is currently undergoing phase II clinical trials in combination with chemotherapy for the treatment of prostate cancer, NSCLC and breast cancer. In 2001, OncoGeneX Technologies and Isis Pharmaceuticals established a co-development and commercialization agreement for the compound. OGX-011 combines OncoGeneX's proprietary antisense position in inhibitors of clusterin with Isis's proprietary second-generation antisense chemistry. The secretory protein clusterin acts as a cell survival protein and is overexpressed in several cancers, including prostate, renal, bladder, lung, ovarian and urothelial cancer, in response to chemotherapy, hormone ablation, radiation therapy and other tumor-killing strategies. By inhibiting clusterin, OGX-011 is intended to enhance the effects of drug therapies in the treatment of the disease.

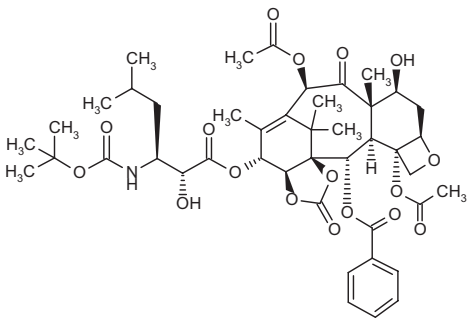
OncoVEX$^{GM\text{-}CSF}$

BioVex's lead oncolytic engineered herpes simplex virus (HSV) OncoVEX$^{GM\text{-}CSF}$ is a therapeutic vaccine 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 primary and metastatic tumor deposits. Phase I/II clinical trials of the vaccine have been completed in several solid tumors, including breast and gastrointestinal cancer, and 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 therapies, such as chemotherapy or radiotherapy, for the treatment of cancer.

OPT-22

OPT-22 is a novel synthetic vaccine that is being evaluated in early clinical trials at Optimer Pharmaceuticals for the treatment of breast cancer.

Ortataxel



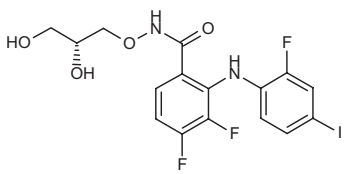
A semisynthetic microtubule-stabilizing antimitotic drug belonging to the chemical class known as the taxanes, ortataxel (Bay-59-8862, IDN-5109) was discovered by Indena and licensed to Bayer in 2000. Pursuant to the

agreement, Bayer gained exclusive worldwide clinical development and commercialization rights to ortataxel and its derivatives while Indena is responsible for extracting and producing the compound worldwide. Bayer has completed several phase II trials for various indications, including breast cancer, renal cell carcinoma, NSCLC and NHL.

p53-DC Vaccine

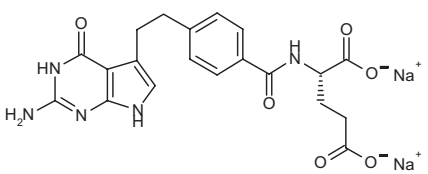
The p53-DC vaccine consists of autologous dendritic cells loaded with a cocktail of three wild-type (R9V, L9V, G11V) and three modified (S9Vm, K9Vm, Y9Lm) HLA-A2-binding p53 peptides and a pan-MHC class II peptide (PADRE). It is undergoing phase I/II clinical trials at the University of Copenhagen and 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.

PD-325901



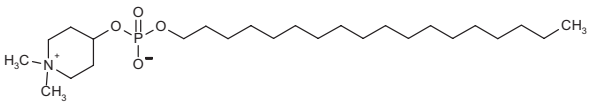
PD-325901 is a mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) (MEK) inhibitor in phase II clinical trials at Pfizer for the oral treatment of NSCLC and in phase I/II trials for the oral treatment of advanced breast cancer, colorectal cancer and melanoma. Stemming from the promising preclinical efficacy and good clinical tolerability but insufficient clinical efficacy of the first MEK inhibitor, CI-1040, Pfizer researchers commenced a search for more potent MEK inhibitors with more favorable properties, leading to the discovery of PD-325901 as a significantly more potent and pharmaceutically improved analogue.

Pemetrexed Disodium



Pemetrexed disodium (Alimta®) was launched in the U.S. in 2004 by Lilly for the second-line treatment of locally advanced or metastatic NSCLC after prior chemotherapy and for the treatment of malignant pleural mesothelioma in combination with cisplatin. Discovered at Princeton University, pemetrexed is a pyrrolopyrimidine analogue of folic acid that simultaneously blocks three separate enzyme targets vital to the survival of cancer cells —thymidylate synthase, dihydrofolate reductase (DHFR) and glycinamide ribonucleotide transformylase (GARFT, phosphoribosylglycinamide formyltransferase)— and demonstrates moderate inhibitory activity against two other folate-requiring enzymes. Treatment includes vitamin supplementation with folic acid and vitamin B_{12}, a vitamin regimen that significantly reduces the drug's side effects without negatively impacting its anticancer properties. Pemetrexed disodium is approved in the E.U. for the same FDA-approved indications. Lilly is conducting a phase III trial of the drug in combination with gemcitabine for the treatment of pancreatic cancer. Several phase II trials are under way by the NCI and Lilly to develop pemetrexed as monotherapy or in combination with other chemotherapeutics for the treatment of breast, colorectal, bladder, cervical, endometrial and ovarian cancer and sarcoma. In 2001, the FDA granted pemetrexed sodium orphan drug designation for the treatment of malignant pleural mesothelioma.

Perifosine



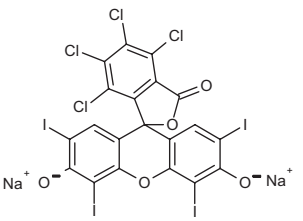
The oral alkylphosphocholine protein kinase B (PKB/Akt) inhibitor perifosine (KRX-0401) has antitumor properties mediated by disruption of lipid-mediated signal transduction pathways, including MAPK and *c*-Jun *N*-terminal kinase (JNK), required for tumor cell growth and survival. The compound has demonstrated 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 has conducted several trials as well. Indications evaluated include melanoma, sarcoma, multiple myeloma, refractory NSCLC, breast cancer (male and female), pancreas, head and neck cancer and prostate cancer and other solid tumors. In 2002, originator AEterna Zentaris granted Access Oncology an exclusive license for the development and marketing of perifosine in the U.S., Canada and Mexico. Following the acquisition of Access Oncology in 2004, Keryx acquired three clinical-stage compounds, including perifosine.

Pertuzumab

Pertuzumab (R-1273, 2C4, Omnitarg™) is a recombinant humanized monoclonal antibody in phase II devel-

opment by Genentech and Roche for the treatment of ovarian cancer. Roche and the NCI are also testing the antibody in phase II trials for the treatment of HER2-overexpressing metastatic breast cancer in combination with trastuzumab. In addition, preclinical studies and early clinical trials are under way at Chugai for the treatment of solid tumors and NSCLC, respectively. Pertuzumab is the first in a new class of targeted therapeutic agents known as HER dimerization inhibitors (HDI), designed to inhibit tumor growth and survival due to the antibody's binding to the dimerization domain of HER2, thereby directly inhibiting the ability of HER2, the most common pairing partner, to dimerize with other HER receptor proteins, and in turn preventing the activation of HER signaling pathways. The compound may have several applications, as HER dimerization is implicated in a number of tumor types. The antibody also has the potential to be used in cancers with normal levels of HER2. In 2003, Roche and Chugai established a license agreement pursuant to which Chugai obtained exclusive rights in Japan to develop and market pertuzumab and bevacizumab, both discovered by Genentech and licensed exclusively to Roche outside the U.S. Pertuzumab is under joint development by Genentech and Roche in the U.S. and Europe.

PV-10



Provectus is conducting early clinical trials of PV-10 gel for the topical treatment of psoriasis and actinic keratosis. An intralesional injectable formulation is also in early clinical development for the therapy of breast cancer and melanoma. The company is seeking approval in the U.S. to begin clinical evaluation of this formulation for the treatment of liver and prostate cancer. The drug's mechanism of action is believed to entail the formation of free radicals upon activation, which eliminate diseased cells. PV-10 concentrates in tumors at cytotoxic levels while quickly dissipating from healthy tissue. Simultaneously, the drug triggers an immune response that can eliminate metastatic tumor tissue.

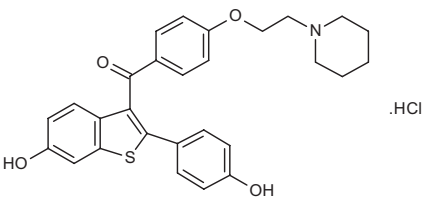
PX-104.1

PX-104.1 (HER2 Protein AutoVac™) is a HER2 protein vaccine in phase II clinical trials at Pharmexa for the treatment of metastatic breast cancer. A phase II trial is under way to test a formulation incorporating QS-21, a proprietary adjuvant licensed to Pharmexa from Antigenics in January 2005, following evidence of efficacy in a phase II trial using a weak adjuvant. The PX-104.1 molecule is a HER2 antigen modified to include two promiscuous and highly immunogenic peptides derived from tetanus toxin, and is designed to overcome tolerance to HER2 and induce effective anti-HER2 polyclonal antibody responses in breast cancer patients where HER2 is overexpressed.

R-1550

Based on the humanized monoclonal antibody HMFG1 that targets most common epithelial cancers, R-1550 is currently undergoing early clinical trials at Roche for the treatment of metastatic breast cancer. R-1550 works by targeting and binding to the MUC1 protein specifically expressed on the surface of cancer cells. Originally developed at Cancer Research UK, the antibody was subsequently developed by Antisoma following the adoption by the company of a clinical program from the Imperial Cancer Research Fund (ICRF) in 2000. In November 2002, Antisoma licensed the worldwide marketing rights for the compound to Roche as part of an alliance.

Raloxifene Hydrochloride



Raloxifene hydrochloride is a SERM that was launched by Lilly in 1998 as Evista® for the prevention of osteoporosis. Currently, the drug is in phase III trials at the company for reducing the risk of invasive breast cancer in postmenopausal women with known heart disease or at high risk for a heart attack, and for the secondary prevention of coronary events in the treatment of coronary artery disease. The NCI is also sponsoring a phase III trial comparing raloxifene and tamoxifen for breast cancer prevention in postmenopausal women. The National Cancer Research Institute is evaluating the combination of raloxifene and goserelin for preventing breast cancer in women with a family history of the disease. In 2005, the compound was assigned orphan drug designation by the FDA for reducing the risk of breast cancer in postmenopausal women.

Ranpirnase

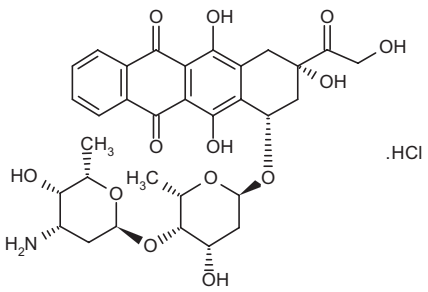
Ranpirnase (Onconase®) is a ribonuclease isolated from the eggs of *Rana pipiens*, the leopard frog. The drug, a single peptide chain containing 104 amino acids, degrades RNA and interrupts protein synthesis, resulting in the inhibition of cell growth and the induction of apop-

tosis. Ranpirnase is in phase III development by Alfacell for the treatment of unresectable malignant mesothelioma both as monotherapy and in combination with doxorubicin. The compound is also in phase I/II trials for the treatment of NSCLC and phase II studies are expected to commence this year for renal cell and breast cancer. Ranpirnase overcomes multidrug resistance, the main cause of systemic chemotherapy failure, as well as other forms of drug resistance. Alfacell expanded its research collaboration with the NCI in 2002, whereby the NCI will evaluate ranpirnase as a radiation enhancer and will determine the effects of ranpirnase on pO2 and *in vivo* growth delay. In 2002, Alfacell established a new collaborative research program with the University of Frankfurt that focuses on ranpirnase as a treatment for various forms of childhood soft tissue and muscle cancer. Ranpirnase was granted fast track designation for malignant mesothelioma by the FDA in 2003 and the compound was granted orphan medicinal product status in Europe in February 2001 for the same indication.

rhIGFBP-3

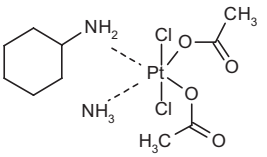
The recombinant human insulin-like growth factor binding protein rhIGFBP-3 is in phase I clinical studies at Insmed in order to identify the appropriate dose for a planned phase II trial. The protein may have potential in the treatment of breast, colon, lung and prostate cancer. Several lines of evidence from various cell systems have suggested that IGFBP-3 may play a more active, IGF-independent role in the growth regulation of cancer cells, binding specifically with high affinity to the surface of various cell types and directly inhibiting monolayer growth of these cells in an IGF-independent manner. Recent independent studies have demonstrated that IGFBP-3 can enhance and even synergistically increase the efficacy of standard cancer therapies. For example, paclitaxel-induced apoptosis was accentuated by IGFBP-3, and the compound has been shown to sensitize cells to apoptotic signals such as irradiation and ceramides.

Sabarubicin Hydrochloride



Sabarubicin hydrochloride, a disaccharide analogue of doxorubicin, is a potent DNA topoisomerase II inhibitor in phase II development at Menarini for the treatment of breast, lung, ovarian and prostate cancer and sarcoma. In 2004 Menarini received orphan drug status from the EMEA for sabarubicin for the treatment of small cell lung cancer.

Satraplatin



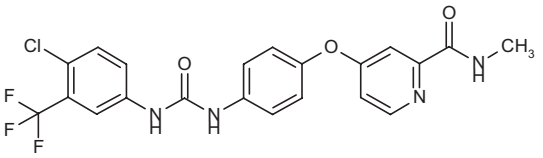
The first orally administered platinum compound, satraplatin, was discovered by Johnson Matthey and licensed to Spectrum Pharmaceuticals in 2001. A third-generation platinum derivative, satraplatin has better bioavailability in comparison to cisplatin and carboplatin, other platinum anticancer drugs also developed in part by Johnson Matthey. In preclinical models, the antitumor activity of the drug was comparable to cisplatin and carboplatin, with less crossresistance. Satraplatin binds to the DNA of cancer cells, thereby blocking cell division. In 2002, GPC Biotech acquired an exclusive worldwide license to satraplatin from Spectrum. A rolling NDA has been filed for the drug in the U.S. as a second-line treatment for hormone-refractory prostate cancer (HRPC) in combination with prednisone. Phase II trials are being conducted by Johnson Matthey and GPC Biotech for the treatment of small cell lung cancer and relapsed ovarian cancer. Additional phase II trials at GPC Biotech are evaluating its potential for the oral treatment of metastatic breast cancer. Furthermore, a phase I/II trial testing the drug in combination with radiation in patients with locally advanced NSCLC is ongoing at the company. Spectrum is studying satraplatin in combination with paclitaxel (Taxol®) as a first-line therapy in patients with unresectable advanced NSCLC. GPC Biotech is also conducting early clinical trials of satraplatin in combination with docetaxel (Taxotere®) for the treatment of solid tumors. The FDA granted fast track designation to satraplatin as second-line treatment for patients with HRPC in 2003. In 2005, Pharmion and GPC Biotech established a co-development and license agreement for satraplatin, pursuant to which Pharmion gained exclusive commercialization rights for Europe, Turkey, the Middle East, Australia and New Zealand, while GPC Biotech retains rights for the North American market and all other territories.

SaveCream®

SaveCream® is an aromatase inhibitor in phase II clinical development at Medical Discoveries for the topical treatment of breast cancer. Estradiol is produced in significant quantities from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Reducing circulating estradiol levels

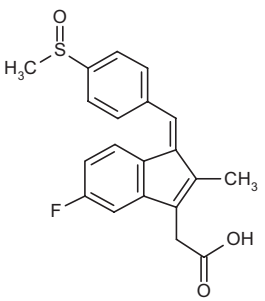
has been shown to produce a beneficial effect in women with breast cancer. SaveCream® was originally developed at SaveTherapeutics. Medical Discoveries completed the acquisition of the intellectual property assets from SaveTherapeutics in 2005 and is in the process of developing a global commercialization strategy for the product candidate.

Sorafenib



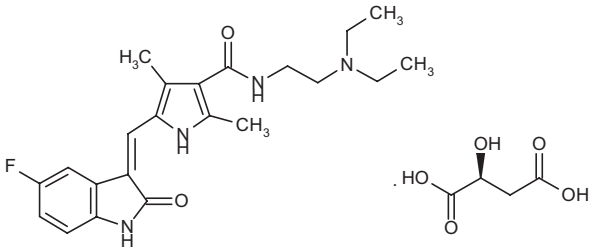
Sorafenib (Nexavar®), an oral multitargeted kinase inhibitor that targets serine/threonine and receptor tyrosine kinases in both the tumor cell and tumor vasculature, was approved in the U.S. in 2005 for the treatment of advanced metastatic renal cell carcinoma. An MAA has been filed in the E.U. seeking approval for this indication and filings have also been completed in Switzerland, 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. The drug is being evaluated in phase III trials for the treatment of advanced hepatocellular carcinoma and metastatic melanoma. Bayer is conducting phase II trials with sorafenib as first-line therapy for the treatment of renal cell carcinoma. In addition, the NCI is evaluating the compound both as a single agent and in combination with other oncology agents in phase II trials for several indications, including metastatic breast, head and neck, ovarian, pancreas, prostate, uterine and thyroid cancer and NSCLC, as well as malignant mesothelioma. An NCI-sponsored phase I trial is ongoing for the treatment of anaplastic astrocytoma and glioma, including glioblastoma. In 2004, orphan drug status was granted by the FDA and the EMEA for the treatment of renal cell carcinoma.

Sulindac



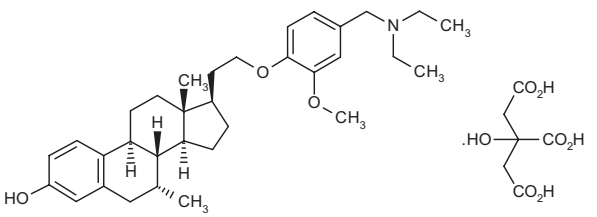
The nonsteroidal antiinflammatory drug (NSAID) sulindac has been available for more than 30 years as an antiinflammatory and analgesic agent for use in treating osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The drug is also available for the treatment of acute painful shoulder and gout. Clinical studies are under way at the NCI to determine the potential of the NSAID for the prevention of oral cancer and breast cancer. A trial evaluating the combination of tamoxifen with sulindac for the treatment of desmoid tumor is also under way at the NCI.

Sunitinib Malate



In February 2006, sunitinib malate (SU-11248, Sutent), the first in a class of orally active, multitargeted tyrosine kinase inhibitors originally developed by Sugen and acquired by Pfizer following Pfizer's acquisition of Pharmacia in 2003, was launched in the U.S. for two indications: the treatment of GISTs and metastatic renal cell carcinoma in patients whose tumors do not respond to or do not tolerate standard treatment. The company is evaluating sunitinib in phase II trials for the treatment of liver, metastatic breast, prostate and neuroendocrine cancer, metastatic NSCLC and renal cell carcinoma in patients with bevacizumab-refractory metastatic disease. Tyrosine kinase inhibitors are antineoplastic and antiangiogenic agents, targeting tumors by inhibiting the blood supply and vascular cells by interfering with the chemical pathways essential for tumor survival.

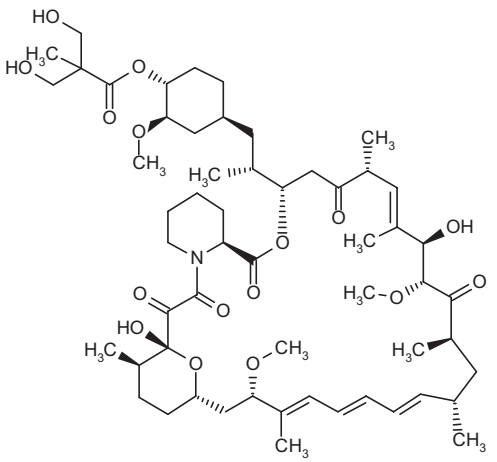
TAS-108



Taiho's TAS-108 (SR-16234) oral solution is a SERM in phase I trials in Japan and phase II clinical trials in the U.S. for the treatment of metastatic breast cancer. In addition to its antitumor activity, the drug appears to exert protective effects on bone and the cardiovascular system. The drug candidate has been shown to suppress the transcriptional activation of the estrogen receptors ERα and ERβ, acting as a full estrogen antagonist, compared to the partial activity seen for tamoxifen and raloxifene. Like other full estrogen antagonists, TAS-108 is able to overcome tamoxifen resistance caused by an ERα mutation.

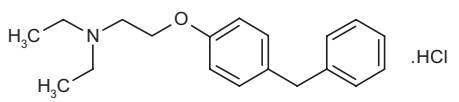
Additionally, the compound recruits a co-repressor, SMRT (silencing mediator for retinoid and thyroid hormone receptor), to help inhibit estrogen receptor activity. TAS-108 was originally developed at SRI and later became the subject of a co-development agreement with Taiho. In July 1999, Taiho obtained exclusive worldwide rights to develop and market the drug.

Temsirolimus



Temsirolimus (CCI-779) is a cell cycle inhibitor in phase III trials at Wyeth for the treatment of renal cell carcinoma and mantle cell lymphoma. The company discontinued development of an oral formulation for the treatment of metastatic breast cancer earlier this year. Phase II trials are also being conducted by Wyeth for the treatment of endometrial cancer and squamous cell carcinoma of the head and neck, as well as phase I studies for prostate cancer, and the NCI is evaluating temsirolimus in phase I and II clinical trials for the treatment of several other types of cancer, including NSCLC, lymphoma, CML, endometrial cancer, multiple myeloma, CLL, NHL, glioma and solid tumors in pediatric patients. Temsirolimus is also the subject of phase II trials at Wyeth for its potential in the treatment of multiple sclerosis and rheumatoid arthritis. Temsirolimus works by inhibiting mTOR-driven cell proliferation and it also has the potential to block the inflammatory responses related to autoimmune diseases by blocking T-cell proliferation. In 2004, the FDA granted temsirolimus orphan drug designation for the treatment of renal cell carcinoma.

Tesmilifene Hydrochloride

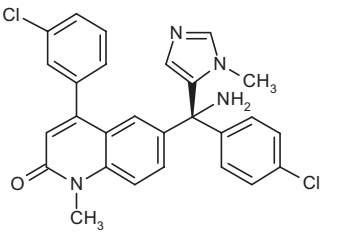


Tesmilifene hydrochloride, a small-molecule chemopotentiator, is in phase III clinical trials in combination with various chemotherapies for the treatment of metastatic and recurrent breast cancer. Tesmilifene combination phase II studies are also under way for the treatment of prostate cancer. Originally developed at the University of Manitoba and CancerCare Manitoba, the compound was licensed to YM Biosciences in 2000. Additionally, in 2005, YM Biosciences established a partnership with Shin Poong Pharmaceutical to expand the development program for tesmilifene into gastric cancer. Tesmilifene has been granted fast track designation in the U.S. for the treatment of women with advanced breast cancer in combination with anthracycline chemotherapies.

Theratope®

Theratope® in combination with chemotherapy is in phase III and II clinical development at Biomira for the treatment of metastatic breast cancer and metastatic colorectal cancer, respectively. The working hypothesis for this cancer vaccine is that it stimulates the generation of an immune response to the tumor-associated sialyl-Tn epitope, which leads to a therapeutic effect. Further development of Theratope® by Biomira is pending the commitment of a collaborative partner.

Tipifarnib



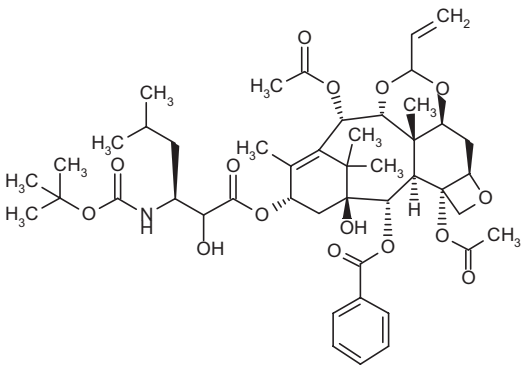
Tipifarnib (R-115777, Zarnestra™), discovered and developed at Johnson & Johnson, is an oral inhibitor of farnesyltransferase, an enzyme required for activation of multiple tumor growth pathways. Johnson & Johnson is exploring with the NCI potential uses of tipifarnib in solid and hematological malignances. Phase III trials are in progress at the NCI and J&J for the treatment of patients with AML in remission and in newly diagnosed AML. Phase II trials are ongoing at J&J in combination with radiotherapy for glioblastoma multiforme and at the NCI for the treatment of malignant melanoma, sarcoma and relapsed or refractory lymphoma, and phase I/II trials of tipifarnib are also under way at the NCI for the treatment of glioma, relapsed multiple myeloma and myelodysplasia. Early clinical studies are evaluating the potential of tipifarnib in combination with radiation and/or other chemotherapy for the treatment of NSCLC, pancreatic cancer, metastatic or locally advanced breast cancer and AML. Additional early combination studies are ongoing at the M.D. Anderson Cancer Center for the treatment of CML in combination with imatinib. Johnson & Johnson received a not approvable letter from the FDA in June

2005 for the treatment of patients 65 years of age and older with newly diagnosed AML, although the drug had been granted orphan drug designation by the FDA for the treatment of AML in 2004. In 2005, the Committee for Orphan Medicinal Products of the EMEA adopted a positive opinion on orphan medicinal product designation for the drug.

Tocosol™ Paclitaxel

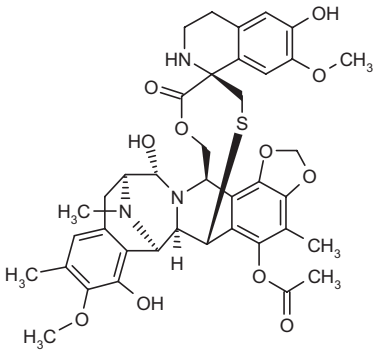
Tocosol™ paclitaxel (S-8184) is a microtubule-stabilizing agent currently in phase III trials for the treatment of metastatic breast cancer. The product is being developed for this indication by Sonus and licensee Schering AG. Schering acquired exclusive worldwide rights to the product in October 2005. Sonus is also conducting or has conducted phase II trials for the treatment of bladder cancer, NSCLC and ovarian cancer. Tocosol™ paclitaxel is a novel ready-to-use reformulation of paclitaxel that does not require reconstitution, dilution or preparation as with currently marketed paclitaxel products. It is administered as a 15-min infusion, compared to the prolonged 3-h infusion required with available paclitaxel products. Sonus's Tocosol™ technology uses vitamin E and vitamin E derivatives to solubilize, stabilize and formulate drugs with the goal of enhancing their delivery, safety and efficacy. The FDA has assigned fast track and orphan drug designation to the product for the treatment of metastatic or locally advanced inoperable transitional cell carcinoma of the urothelium, the most common form of bladder cancer.

TPI-287



Tapestry Pharmaceuticals' TPI-287 is a novel third-generation taxane in phase I clinical development as a potential treatment for breast, small cell lung, ovarian, pancreatic and prostate cancer and neuroblastoma. TPI-287 is designed to overcome acquired resistance to taxane-based therapies by circumventing MDR1. Preclinical studies have demonstrated that this compound is substantially more potent than paclitaxel in paclitaxel-resistant tumors and is at least as potent as paclitaxel in treatment-naïve tumors.

Trabectedin

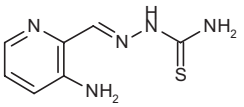


Trabectedin (ET-743, Yondelis®) is a novel marine-derived tetrahydroisoquinoline antitumor agent isolated from the colonial tunicate *Ecteinascidia turbinate*. The drug binds to the DNA minor groove, bending the DNA towards the major groove and blocking the activation of genes in a unique way via several pathways, including selective inhibition of the expression of key genes (including oncogenes) involved in cell growth and drug resistance, inhibition of genetic repair pathways and inhibition of cell cycle progression leading to *p53*-independent programmed cell death. Trabectedin is in phase III development by PharmaMar and partner Johnson & Johnson for the treatment of advanced soft tissue sarcoma and ovarian cancer, and the NCI is conducting a phase II study in patients with recurrent or refractory soft tissue sarcoma or Ewing's tumors. PharmaMar is conducting additional phase II trials of trabectedin for several oncological indications, including breast cancer and advanced prostate cancer. Under a 2001 agreement, the J&J subsidiary Ortho Biotech holds marketing rights worldwide with the exception of Europe, where PharmaMar will market the compound. In July 2003, the European CPMP recommended against granting marketing authorization to trabectedin for soft tissue sarcoma. PharmaMar appealed the decision in September 2003, but the CPMP subsequently rejected the appeal. Trabectedin was granted orphan drug designation for the treatment of soft tissue sarcoma by the EMEA in 2001 and by the FDA in 2004. Additional orphan drug designations for the treatment of ovarian cancer were granted in 2003 in the E.U. and in 2005 in the U.S.

Trastuzumab-DM1

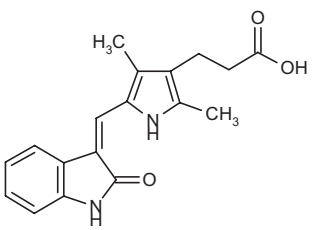
Trastuzumab-DM1 is a tumor-activated prodrug (TAP) immunoconjugate comprising Genentech's therapeutic antibody, the humanized anti-HER2 antibody trastuzumab (Herceptin®), and ImmunoGen's antimitotic maytansinoid DM1. Trastuzumab targets overexpression of the HER2 protein, which is associated with approximately 20% of all breast cancers. In late 2005, Genentech filed an IND seeking FDA clearance to begin clinical evaluation of trastuzumab-DM1.

Triapine®



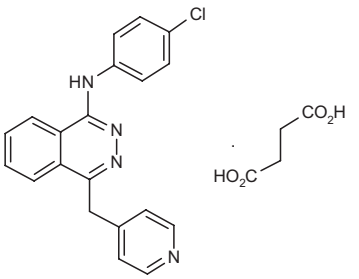
A small-molecule ribonucleoside-diphosphate reductase inhibitor discovered by Yale University and licensed to Vion, Triapine® inhibits DNA synthesis and DNA repair, thereby increasing the antitumor effects of many common anticancer drugs, such as cisplatin, cyclophosphamide and etoposide. Vion is conducting phase II trials of triapine in combination with gemcitabine for the treatment of pancreatic cancer. Additional phase II trials in combination with other chemotherapeutic agents are under way at the NCI for the treatment of gallbladder, ovarian and metastatic breast cancer and NSCLC. The NCI is carrying out early clinical trials of Triapine® in combination with radiation therapy in unresectable pancreatic cancer and with other chemotherapeutic agents for the treatment of lymphoma and advanced and metastatic or refractory solid tumors or lymphoma. In 2003, Vion established an agreement which granted Pason exclusive rights to develop, manufacture and market triapine for anticancer and antiviral indications in China, Taiwan, Hong Kong and Macao.

TSU-68



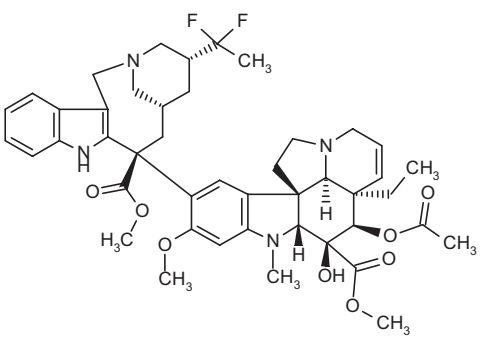
TSU-68 (SU-6668) is an angiogenesis inhibitor in phase II clinical trials at Taiho for the oral treatment of breast cancer. The drug candidate is a novel, potent small-molecule inhibitor of the following receptor tyrosine kinases: VEGFR-2, PDGFR and FGFR. In preclinical trials, tumor response to TSU-68 was correlated with high levels of VEGF expression and tumor vascularity. The decrease in tumor vessel density after treatment with the drug was strongly correlated with antitumor activity and was due to endothelial cell apoptosis caused by inhibition of VEGF signaling. TSU-68 was originally developed at Sugen, a subsidiary of Prizer. In July 1998, Sugen and Taiho established an agreement in Japan for the development and commercialization of Sugen's angiogenesis inhibitors, including TSU-68. Sugen discontinued development of an oral formulation for the treatment of solid tumors earlier this year.

Vatalanib Succinate



Vatalanib succinate (PTK-787, ZK-222584) is a novel once-daily oral angiogenesis inhibitor discovered by Novartis that blocks the signaling of all known VEGF pathways at the receptors (VEGFR-1, VEGFR-2 and VEGFR-3) regardless of the growth factor (VEGF-A-E). The drug as monotherapy or in combination with other chemotherapeutic agents is in phase III development by Novartis and development partner Schering AG for the first- and second-line treatment of metastatic colorectal cancer. Phase II trials are under way at Novartis and the NCI in combination with letrozole for the treatment of breast cancer in postmenopausal women. Schering AG is also developing vatalanib in phase II clinical trials in patients with stage IIIB/IV NSCLC and glioblastoma. Additional phase II development is under way at the NCI for the treatment of myelodysplastic syndromes. The NCI, Novartis and Schering AG are conducting phase I/II clinical trials with vatalanib in combination with other chemotherapeutic agents for the treatment of solid tumors. Novartis and the NCI are also performing phase II clinical trials for the treatment of prostate cancer and multiple myeloma, and phase I/II trials in patients with refractory AML, blastic phase CML and agnogenic myeloid metaplasia in combination with imatinib. The compound in combination with gemcitabine and verteporfin is also in phase I/II trials at Novartis for the treatment of pancreatic cancer and macular degeneration, respectively.

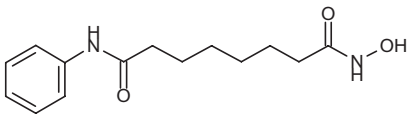
Vinflunine



Vinflunine (Javlor™) is a second-generation bifluorinated analogue of the *Vinca* alkaloid vinorelbine. The *Vinca* alkaloids are antimitotic agents known to inhibit mitotic assembly via tubulin polymerization inhibition. Vinflunine is in phase III trials at Pierre Fabre and Bristol-

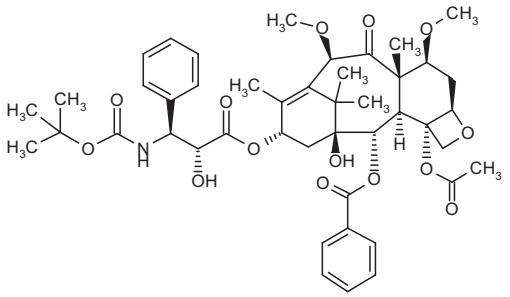
Myers Squibb for the treatment of bladder cancer. Moreover, Bristol-Myers Squibb is conducting phase II trials with vinflunine for the treatment of metastatic breast cancer and small cell lung cancer. Pursuant to a 2004 agreement, Bristol-Myers Squibb holds an exclusive license to vinflunine in the U.S., Canada, Japan, Korea and certain South East Asian markets, while Pierre Fabre is responsible for the development and marketing of the product in all other countries, including Europe.

Vorinostat



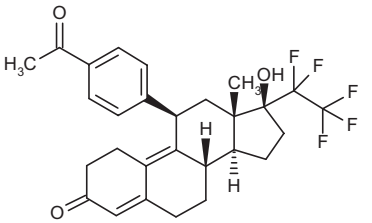
Vorinostat (suberanilohydroxamic acid, MK-0683, SAHA) is a cytodifferentiating agent and a histone deacetylase inhibitor in phase II clinical development at Merck & Co. for the treatment of CTCL, specifically mycosis fungoides and Sezary syndrome. Vorinostat has shown broad antitumor activity in both solid and hematological malignancies and phase III trials are under way at the company and the NCI with the drug candidate for the treatment of malignant mesothelioma, as well as phase II studies in NSCLC. Phase II clinical trials are under way at the NCI for the treatment of metastatic breast cancer in women and men, kidney cancer, glioblastoma multiforme, melanoma, thyroid cancer, AML and NHL. Early clinical trials are ongoing at Merck and the NCI to evaluate the drug's potential in the treatment of a variety of other solid tumors and hematological malignancies. Vorinostat has been shown to induce transcriptional activation, cell differentiation and growth inhibition. The drug candidate has been assigned orphan drug designation by the FDA for the treatment of multiple myeloma, mesothelioma and T-cell NHL, as well as fast track status. Merck added vorinostat to its product pipeline following the company's acquisition of Aton Pharma in 2004.

XRP-6258



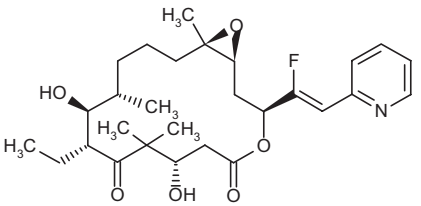
Phase II clinical trials are in progress at Sanofi-Aventis with the antimitotic agent XRP-6258 for the treatment of taxane-resistant metastatic breast cancer. The drug acts by promoting tubulin assembly and stabilizing microtubules against depolymerization. The taxoid displays potent and broad-spectrum antitumor activity *in vitro* and *in vivo*, and unique characteristics including activity against MDR1-expressing tumors, lack of cross-resistance with standard antitumor agents and the ability to cross the blood-brain barrier.

ZK-230211



ZK-230211 (ZK-PRA) Is a synthetic antiprogesterone agent in early clinical trials at Berlex for the treatment of breast cancer. Preclinical studies suggested that the compound blocked tumor growth and initiated tumor cell apoptosis in progesterone receptor-expressing breast tumors. ZK-230211 is the product of a joint development agreement between Berlex, a subsidiary of Schering AG, and Jenapharm.

ZK-EPO



ZK-EPO (ZK-219477), a fully synthetic epothilone, is in phase II clinical development at Schering AG and its U.S. affiliate Berlex for the treatment of ovarian cancer, metastatic breast cancer, SCLC, prostate cancer and NSCLC. A highly potent microtubule stabilizer that accumulates preferentially in the nucleus of cells, ZK-EPO is designed to have improved efficacy and safety compared to currently available chemotherapeutic agents. The compound exhibits significant efficacy across a broad spectrum of tumor models *in vivo*, including those resistant to widely used chemotherapeutic agents, such as the taxanes and anthracyclines, as well as a favorable safety profile.