INVESTIGATIONAL THERAPIES

NILOTINIB
(AMN107; TASIGNA™)

I. MECHANISM OF ACTION
Nilotinib is a novel aminopyrimidine, available as an oral formulation that is an ATP-competitive inhibitor of BCR-ABL, which prevents the activation of bcr-abl dependent mitogenic and anti-apoptotic pathways, leading to the death of the bcr-abl phenotype. It is 10 – 100 times more potent than Imatinib in preclinical models. It is also active in Imatinib resistant cell lines. It is an aniline-pyrimidine derivative structurally related to imatinib.

II. PHARMACOKINETICS
Pharmacokinetic data in humans is pending. Animal PK has been performed. Absorption was moderate with a moderate bioavailability of 34% in rats following a single oral dose. Elimination half-lives of the biphasic plasma profile were 1.5 hours and 116 hours for the rat. It is highly plasma protein bound. The Vd is large – widely distributed to most tissues, with the highest doses found in the stomach, glandular, adrenal, liver and bile. Radioactivity in BM was similar to the blood. There was minimal passage for drug-related radioactivity across the blood:brain and blood:testis barriers.

III. DOSAGE AND ADMINISTRATION
Phase I started at 50 mg PO QD. Doses in clinical trials are currently at 800 mg PO QD.

IV. TOXICITY
Main target organ in rats and dogs appears to be the liver, and adverse events are consistent with hepatocholestatic jaundice. Emesis also occurs.

V. CLINICAL MONITORING: CBC + differential.

VI. DRUG INTERACTIONS
Based on its inhibition for CYP enzymes 2C8, 2C9, 2C19, 2D6, and 3A4/5, nilotinib may inhibit the metabolic clearance of comedications metabolized by these CYP enzymes, if sufficiently high concentrations of nilotinib are achieved *in vivo*.

HuMAX-CD4
(ZANOLIMUMAB™)

I. MECHANISM OF ACTION
HuMax-CD4 is a fully human monoclonal antibody (immunoglobulin IgG1K) targeting the CD4 receptor on T-cells. Excessive proliferation of CD4+ T-cells occurs in cutaneous T-cell lymphoma.

II. PHARMACOKINETICS:
Initial data show non-linear pharmacokinetics.

III. DOSAGE AND ADMINISTRATION
In two phase II the treatment regimen involves a 280 mg, 560 mg or 980 mg dose of HuMax-CD4 once a week for 16 weeks.

V. TOXICITY
HuMax-CD4 is considered to be safe and well tolerated in clinical trials to date.
Five of the 47 patients were treated in the Phase II CTCL safety studies at all dose levels experienced grade three events (hypersensitivity, elevated liver enzymes, aggravated pruritus [2 patients], and muscle fiber rupture).
Infusion related toxicities, fever.

HuMAX-CD20
(OFATUMUMAB™)

I. MECHANISM OF ACTION

HuMax-CD20 is a fully human monoclonal antibody targeting the CD20 receptor on B-cells. It binds to a unique binding site on the CD20 target cells when compared to other CD20 antibodies. HuMax-20 is effective in inducing natural killer cells-mediated cytotoxicity of B-cell tumors. IN a primate study Hu-Max -CD20 effectively depleted B-cells from the blood and lymph nodes. It depleted these B-cells for a period of time 4 times longer than rituximab.

II. PHARMACOKINETICS: Data not available.

III. ADMINISTRATION: Data not yet available.

IV. TOXICITY: Data not available.

LAPATINIB
(GW572016)

I. MECHANISM OF ACTION

Lapatinib is a potent and reversible inhibitor of the tyrosine kinase domains of EGFR and HER2. Lapatinib blocks ATP from binding to the tyrosine kinase domain and inhibits tyrosine kinase from using ATP as a cofactor for phosphorylation of tyrosine residues. Lapatinib also inhibits the activation of cell proliferation effectors such as Erk ½ and AKT.

II. PHARMACOKINETICS

Limited data is available in the public domain. Thought to undergo first-pass metabolism catalyzed by CYP3A4/5. It does not appear to be a substrate for p-glycoprotein. Pharmacokinetics are linear up to a dose of 1800 mg/day. At a dose of 1200 mg/day plasma concentrations that inhibit > 90% EGFR and HER2 are achieved. Steady state concentrations are achieved within 6 – 7 days. Peak serum concentrations are achieved within 3 to 6 hours following dose administration. Serum concentrations increase with increasing dose.
Reference: Burris HA, et al. *J Clin Oncol* 2005;23:5305 – 13.

III. DOSAGE AND ADMINISTRATION

Adminisered orally. Doses of 500 to 1650 mg daily have been studied.

IV. TOXICITY

The most frequency adverse events in clinical trials include diarrhea (42%), rash [rash, acne, dermatitis acneiform] (31%), nausea (13%), and fatigue (10%).
Reference: Nelson MH, Dolder CR. *Ann Pharmacother* 2006;40:261 – 9.

LONAFARNIB
(SCH66336)

I. MECHANISM OF ACTION
Lonafarnib is a tricyclic nonpeptidomimetic compound that selectively inhibits farnesyltransferase. Farnesyltransferase catalyzes the activation of the p21 protein that is encoded by Ras genes and has GTPase activity and participates in signal transduction. Mutations in the Ras genes can result in unregulated cell proliferation and are commonly found in human cancers. Thus, by inhibiting farnesyltransferase, lonafarnib inhibits cell proliferation. Lonafarnib may also enhance tumor cell sensitivity to chemotherapy.

II. PHARMACOKINETICS
Half-life is approximately 3.5-10 hours.

III. DOSAGE AND ADMINISTRATION
Administered orally. Doses: Combination therapy: 100 mg PO BID; Monotherapy: 200 mg PO BID. Lonafarnib should be taken with food.

IV. TOXICITY
Diarrhea; nausea/vomiting; anorexia; neutropenia; thrombocytopenia; neurotoxicity - disorientation and confusion; transient elevation of LFTs; transient elevation of SCr.

OBLIMERSEN
(GENASENSE®)

I. MECHANISM OF ACTION

Oblimersen is an oligonucleotide, which works via an antisense mechanism. It binds to Bcl-2 messenger RNA, resulting in decreased formation of Bcl-2 (a protein that inhibits apoptotic cell death and is over-expressed in many tumor cells). Bcl-2 may also be a cause of chemotherapy resistance. Oblimersen results in increased tumor cell death and increased chemotherapy sensitivity.

II. PHARMACOKINETICS

A) 85% protein bound with a volume of distribution of ~0.28 L/kg; total clearance 6.09 L/hour.
B) Metabolized via exonuclease-mediated cleavage to shortened oligonucleotides and mononucleotide metabolites. Css achieved within 10 hours.
C) Elimination half-life is approximately 2 hours.
D) Metabolites are excreted primarily in the urine.

III. DOSAGE AND ADMINISTRATION

Malignant melanoma, multiple myeloma, lung cancer: 7 mg/kg/day CIVI for 5 days, repeated every 21 days (current protocol submitted to FDA for NDA). Refractory CLL: 3 mg/kg/day CIVI for 7 days, repeated every 21 days.

IV. TOXICITY

As reported in a randomized phase III trial comparing dacarbazine vs. dacarbazine + oblimersen in patients with melanoma: Fever (3.1 vs 5.9%); Grade 3-4: neutropenia (12.5 vs 21.3%); thrombocytopenia (3.9 vs 7.5%); anemia (4.7 vs 7%); Nausea (2/5 vs 7%); Fatigue; Elevation of LFTs.

RUBITECAN
(ORATHECIN™)

I. MECHANISM OF ACTION

Rubitecan (9-nitrocamptothecin) is a water-insoluble topoisomerase I inhibitor. It has shown greater activity in human cancer xenografts in nude mice than the parent compound, camptothecin, and the water-soluble camptothecin derivatives topotecan and irinotecan. Camptothecin and its derivatives are indole alkaloids and form a reversible complex with topoisomerase I covalently bound to DNA, which subsequently prevents DNA replication and transcription and leads to cell death by apoptosis. The closed-ring lactone form of camptothecins appears responsible for antineoplastic activity. Preclinical antitumor activity has been substantially greater in cells in the S-phase compared to other phases, and during prolonged exposure to these agents. In vitro data reveal that rubitecan also has the ability to inhibit replication of the HIV-1 virus.

II. PHARMACOKINETICS

A) Rubitecan is metabolized in plasma and the liver to 9-aminocamptothecin (9-AC) and other metabolites; although 9-AC is active, its concentrations in plasma are low and rubitecan is the predominant active form in plasma.
B) Food greatly affects bioavailability; increased bioavailability under fasting conditions.
C) Following an oral dose of rubitecan, peak concentrations of total drug (rubitecan plus metabolites, including 9-AC) usually occur within 8 hours.
D) Approximately half of an oral dose is excreted in the urine as rubitecan/metabolites.
E) An elimination half-life of 11 hours has been reported for total drug in plasma.
F) Systemic absorption occurs after aerosol doses of liposomal rubitecan.
G) Rubitecan and its metabolite 9-aminocamptothecin are insoluble in water.

III. DOSAGE AND ADMINISTRATION

A) A dose of 1.5 mg/m^2/day PO for 5 days followed by 2 days of rest for 8 consecutive weeks has been used in many cancer trials.
B) Liposomal rubitecan has been given via aerosol for treatment of pulmonary metastases.

IV. TOXICITY

A) Myelosuppression is a reported dose-limiting toxicity. Anemia, thrombocytopenia, and neutropenia are frequent during oral administration 1 to 2 mg/m^2 daily for 4 or 5 days weekly; grade 3/4 incidences in phase I/II studies were approximately 30%, 15%, and 25% respectively. Granulocyte count nadirs generally occur after 2 weeks of treatment, whereas nadirs in hemoglobin were most often seen after 3 weeks.
B) Hemorrhagic chemical cystitis is a complication of oral therapy, reaching grade 2 or higher in up to one-fourth of patients receiving 1 to 2 mg/m^2 daily. Copious fluid intake daily (3 liters) is indicated to minimize the risk of chemical cystitis.
C) Elevations of transaminases, bilirubin, and alkaline phosphatase (all grades) were observed in over 50% of pancreatic cancer patients receiving initial doses of 1.5 mg/m^2 daily for 5 days/week.
D) Nausea, vomiting, anorexia, and diarrhea are common during oral therapy, but grade 3/4 severity is typically seen in less than 15% of patients receiving doses lower than 2 mg/m^2 daily.

SCIO-469

I. MECHANISM OF ACTION

SCIO-468 acts to inhibit p38α MAPK. P38α MAPK activation controls the production of many of the major cytokines that are supportive of the osteolytic environment (such as directly inhibiting IL-6 production; inhibiting IL-1; blocking the synthesis of COX-2; as well as RANL). Inhibition of these multiple factors by SCIO-469 renders the marrow micro-environment less activated, and less supportive of tumor growth, metastasis, drug resistance, and the development of osteolytic lesions.

II. PHARMACOKINETICS

Not available.

III. DOSAGE AND ADMINISTRATION:

The optimum doses determined in Phase IIa was a total daily dose of SCIO-469, administered as 60 mg PO three times daily (doses should be at least 6 hours apart). Maximal ex vivo inhibition of TNFα is observed at doses of 1 mg/kg TID.

IV. TOXICITY

Not available.

TIPIFARNIB; R115777
(ZARNESTRA)

I. MECHANISM OF ACTION
Tipifarnib is a farnesyl transferase inhibitor.

II. PHARMACOKINETICS
A) Not currently available.

III. DOSAGE AND ADMINISTRATION
A) 400 mg PO BID. Available as 100 mg tablets.
B) It should be taken with food to ensure bioavailability. Avoid the use of antacids containing magnesium or aluminum 2 hours prior and 2 hours after the dose.
C) Dose limiting toxicities occurred at a dose of 1200 mg PO BID (central neurotoxicity – ataxia, confusion, and dysarthria).

IV. TOXICITY
A) Myelosuppression.
B) Febrile neutropenia.
C) Photosensitivity.
D) Diarrhea, nausea, and vomiting.
E) Mood alteration, anxiety, agitation, confusion.
F) Sensory neuropathy.
G) Elevated liver function tests.

IV. CLINICAL MONITORING: CBC and differential.

V. DRUG INTERACTIONS:
May interact with other drugs metabolized by the CYP3A4, CYP2A6, CYP2C8, CYP2C9, CYP2C10, and CYP2D6. Enzyme inducing anticonvulsants (e.g., phenytoin, carbamazepine, and Phenobarbital) may decrease serum concentrations of tipifarnib, therefore reducing it's therapeutic efficacy. Change to a non-enzyme inducing anticonvulsant. Tipifarnib is contraindicated in patients with known allergies to imidazoles (e.g., clotrimazole, ketoconazole, and miconazole). There is a potential interaction between tipifarnib and warfarin. Patients have experienced elevated INR's and bleeding with this combination. When using warfarin in patients on tipifarnib, monitor the INR closely. PK data suggest that H2 antagonists and PPI's do not alter the exposure to tipifarnib to a clinically significant extent.

TROXACITABINE
(TROXATYL®)

I. MECHANISM OF ACTION
Troxacitabine is a nucleoside analog, which is structurally related to lamivudine (antiviral agent). Troxacitabine is triphosphorylated and causes chain termination after it is incorporated into DNA.

II. PHARMACOKINETICS
Following bolus administration, troxacitabine exhibits linear PK over a dose range of 0.72 – 10 mg/m^2. Renal excretion is the principal route of elimination with, on average, 69% of the dose excreted unchanged in the urine within 48 hours of a dose.

III. DOSAGE AND ADMINISTRATION:
Various doses and schedules have been evaluated with troxacitabine, ranging from 10 mg/m^2 IV as a 30-mminute infusion to 12 mg/m^2/day as a continuous infusion.

IV. TOXICITY
Myelosuppression is a common adverse event. Skin rahs is the most commonly reported non-hematological adverse event and occurs in up to 44% of patients. Gastrointestinal toxicity is also common including diarrhea (25 – 53%), nausea (27 – 40%), vomiting (0 – 21%), stomatitis (0 – 18%). Troxacitabine commonly causes hand-food (PPE) syndrome.

V. CLINICAL MONITORING
Not know at this time.

VI. DRUG INTERACTIONS
None know at this time.