A number of molecularly targeted agents directed at critical pathways involved in cell survival and cell proliferation have recently entered clinical evaluation in children with cancer. These agents offer the potential for more effective anticancer therapy while diminishing acute and long-term toxic effects. Systematic evaluations of agents such as these are essential if continuing improvements in outcome are to be achieved in children with cancer. Brief summaries of the rationale for conducting studies of several agents in children are provided below. Following these summaries is a listing of phase I, phase I/II, phase II, and pilot studies of these agents in pediatric populations.

**Farnesyltransferase Inhibitors R115777 and SCH66336**

Two farnesyltransferase inhibitors (FTIs) are in clinical evaluation in children with cancer: R115777 (Janssen Pharmaceutica, Inc) and SCH66336 (Schering-Plough, Ltd). Although FTIs were initially developed to inhibit cancer cell growth by blocking farnesylation of Ras and preventing its required localization to the plasma membrane,[1,2] it is increasingly apparent that inhibition of farnesylation of other proteins may contribute to the growth-inhibitory effects of FTIs.[3,4] FTIs show in vitro activity against a range of tumor cell lines.[2,4] The in vivo antitumor activity of FTIs (including regression of some tumors) has been observed against a number of tumor types, including Bcr-Abl-expressing leukemias,[5,6] glioma,[7] pancreatic,[4,8] colorectal cancers,[4] and melanoma.[4]
children.[9] Multiple schedules have been evaluated in adults, but in children the primary schedule studied has been twice daily dosing for 21 days every 4 weeks.[10] In the pediatric solid tumor phase I trial, the maximum tolerated dose was 200 mg/m2, and dose-limiting toxicities at higher doses included grade 4 neutropenia, grade 3/4 thrombocytopenia, grade 3 rash, hypofibrinogenemia, vomiting, and diarrhea.[10]

R115777 was studied in a phase I trial in adults with refractory and relapsed leukemia using the twice-daily-for-21-days schedule.[11] Dose-limiting toxicity occurred at 1,200 mg bid with central neurotoxicity evidenced by ataxia, confusion, and dysarthria. Clinical responses occurred in 10 (29%) of the 34 evaluable patients, including 2 complete remissions. R115777 also induced responses in adult patients with chronic myelogenous leukemia (CML)[12] and myelodysplastic syndrome.[13] SCH66336 has been studied in phase I trials in adults using a variety of schedules.[9] For continuous daily oral administration, the recommended phase II dosage in adults is 200 mg bid,[14] with higher doses causing myelosuppression and neurotoxicity (confusion and disorientation). For both R115777 and SCH66336, inhibition of protein farnesylation has been demonstrated at doses with tolerable toxicity.[10,11,15]

R115777 is under evaluation in children with juvenile myelomonocytic leukemia (AAML0122). Aberrant regulation of the Ras pathway, either by Ras-activating mutations[16] or by inactivating mutations of neurofibromin,[17] is characteristic of some cases of juvenile myelomonocytic leukemia. Supporting evaluation of an FTI against juvenile myelomonocytic leukemia is the observation that cells of this disease cultured in vitro show greater sensitivity to FTI-mediated growth inhibition than do normal myeloid precursor cells.[18] On the other hand, an FTI produced no apparent antileukemic effect in a transgenic murine model of juvenile myelomonocytic leukemia based on homozygous neurofibromin deletion.[19] R115777 is also being evaluated in a phase I trial in children with acute leukemias (1930/ADVL0116), based in part on its activity in adults with acute leukemia.[11]

The Pediatric Brain Tumor Consortium is conducting a phase I evaluation of SCH66336 in children with brain tumors (PBTC-003). The rationale for this study includes the significant antiproliferative effects of FTIs against human malignant glioma cells[20,21] and the in vivo antitumor activity of FTIs against human glioma xenograft models.[7,21] FTIs are of interest for patients with neurofibromatosis 1 because mutations in neurofibromin lead to increased Ras signaling.[22,23] The potential applications of FTIs in this patient population include treatment of plexiform neurofibromas[24] and neurofibromatosis 1-associated malignancies.[25] A trial of R115777 in children and adults with plexiform neurofibromas is ongoing (T99-0090).

**Imatinib Mesylate (Gleevec)**

Imatinib mesylate (STI571, Gleevec [Novartis]) is the first rationally designed molecularly targeted agent approved for a cancer indication. The drug potently inhibits several tyrosine kinases, including c-Abl, c-Kit, platelet-derived growth factor (PDGF) receptor, and the p210Bcr-Abl and P190Bcr-Abl fusion proteins associated with Philadelphia chromosome (Ph)-positive leukemias.[26,27] Imatinib inhibits the growth of cells expressing the Bcr-Abl fusion protein[26] and induces apoptosis of Bcr-Abl-positive cells,[26] showing activity both in vitro[26,28,29] and in vivo.[26,30]

These preclinical observations have been replicated clinically, with high levels of antitumor activity observed for patients with chronic phase CML refractory to or intolerant of interferon-alpha.[31] Single-agent activity was also observed against Ph-positive acute lymphocytic leukemia (ALL) and Ph-positive CML in blast crisis, although the response rates were lower and the duration of response relatively short compared to those achieved against chronic-phase CML.[32] Imatinib is very active against the gastrointestinal stromal tumor, which is associated with activating mutations of the c-Kit receptor.[33,34]

Bcr-Abl expression inhibits the apoptosis induced by cytotoxic agents,[35-39] and this Bcr-Abl-driven chemoresistance is likely a major cause of the poor survival rate of patients with Ph-positive leukemia treated with conventional chemotherapy agents. Inhibition of Bcr-Abl can reverse drug resistance,[40] and imatinib has been shown to potentiate the activity of cytotoxic agents against Bcr-Abl-expressing cells.[41,42] The concept of combining imatinib with known active agents is an important one, because resistance to imatinib as a single agent can develop by multiple mechanisms, including overexpression of the Bcr-Abl fusion protein and mutation of the Bcr-Abl gene.[43-45]

A pediatric phase I study of imatinib in children with Ph-positive leukemia (P9973) has been
Imatinib was well tolerated, and its antileukemic activity in children was similar to that seen in adults. Building upon this phase I experience, a phase II trial of imatinib in children with CML who are refractory to or intolerant of interferon-alpha is being conducted (AAML0123). Given the relatively poor prognosis of children with Ph-positive ALL, a high priority of research in childhood ALL is to define ways in which imatinib can potentiate the effect of conventional chemotherapy. The AALL0031 pilot study combines imatinib in 14-day treatment courses with the different chemotherapy blocks used to treat childhood ALL. Recent results from studies in adults with Ph-positive ALL support the feasibility of combining imatinib with the intensive chemotherapy regimens used to treat Ph-positive ALL.[47]

Imatinib is also being evaluated in a phase II study in children with selected solid tumors (ADVL0122), based on its ability to inhibit the stem cell factor/c-Kit pathway and the PDGF/PDGF-receptor pathway. For example, the PDGF ligand and receptor have been detected in various pediatric cancers including osteosarcoma,[48,49] desmoplastic small round-cell tumor,[50, 51] and synovial cell sarcoma.[52] PDGF-C, which also binds to the PDGF-alpha and -beta receptors,[53] has recently been described as a downstream target of deregulation in EWS-FLI1 transformed cells.[54] C-Kit expression has been noted in Ewing’s Sarcoma,[55] neuroblastoma,[56] and synovial cell sarcoma.[57]

The Pediatric Brain Tumor Consortium is conducting a phase I study of imatinib in children with high-grade gliomas (PBTC-006). The rationale supporting this study includes the in vivo activity of the drug against intracranially implanted brain tumor xenograft models,[58] the expression of the PDGF receptor in a substantial proportion of high-grade gliomas,[59] and the ability of imatinib to inhibit PDGF-receptor activation in brain tissue in preclinical models.[60]

**Proteasome Inhibitor PS-341**

PS-341 (also known as LDP-341 or MLN-341), a dipeptidyl boronic acid derivative, is a potent proteasome inhibitor.[61,62] PS-341 induces apoptosis in vitro at nanomolar concentrations in a variety of cancer types, including some leukemia cell lines[63,64] and multiple myeloma cells.[65] It is active in vivo as a single agent against multiple myeloma, prostate, and lung cancer xenograft models and is also active against murine squamous cell carcinoma models.[66,67] It enhances the cytotoxic activity of conventional anticancer agents[68-71] and radiation.[68,72] The basis of the antitumor activity of PS-341 and of its ability to enhance the activity of other anticancer treatments may result from its ability to inhibit nuclear factor (NF)-kappaB activation.[67,69] Other potentially relevant biological activities include stabilization of p53, p21^{WAF/CIP-1}, and p27^{kip1}, inhibition of angiogenesis, and overcoming bcl-2 protective functions.[63,67,73-76]

PS-341 has been evaluated in several different schedules, including twice weekly dosing for 2 weeks (with 1 week’s rest), twice weekly dosing for 4 weeks (2 weeks’ rest), twice weekly dosing every other week, and weekly dosing for 4 weeks (2 weeks’ rest). The recommended phase II dose for these schedules has ranged from 1.3 to 1.7 mg/m2.[77] Toxicities that limited dose escalation included painful neurosensory toxicity, diarrhea, and fatigue.[77] In phase I studies, antitumor activity was observed against multiple myeloma, prostate cancer, non-small cell lung cancer, and non-Hodgkin lymphoma.[77-79] A phase II trial of PS-341 (1.3 mg/m2 per dose twice weekly ‘ 2 weeks every 3 weeks) in patients with multiple myeloma produced high response rates (approximately 50%) in a heavily pretreated population.[80]

A pediatric phase I trial of PS-341 in children with solid tumors is ongoing (ADVL0015). The rationale for evaluating PS-341 in children primarily rests on data from experiments using other proteasome inhibitors against pediatric cancers and on data concerning the expression of the NF-kappaB pathway in pediatric cancers. The proteasome inhibitor lactacystin induced differentiation of a murine neuroblastoma cell line (Neu 2A).[81] blocked cell-cycle progression of human osteosarcoma cells in vitro,[81] and induced apoptosis in an Ewing’s Sarcoma cell line.[82] A peptidyl aldehyde proteasome inhibitor administered as a single dose induced tumor regression in a murine model of human Burkitt’s Lymphoma.[83] The NF-kappaB pathway is activated in leukemia cells from children with ALL[84] and in Reed-Sternberg cells from patients with Hodgkin disease.[85] In the latter setting, NF-kappaB inhibition is sufficient to induce apoptosis.[85,86]

**Phase II**

**Title:** Phase II Study of R115777, Isotretinoin, Cytarabine, and Fludarabine Followed by Allogeneic Bone Marrow or Umbilical Cord Blood Transplantation in Children With Newly Diagnosed Juvenile Myelomonocytic Leukemia
Protocol Number: COG-AAML0122
Participating Institutions: Children’s Oncology Group
Contact: Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click here
Latest Information: http://www.cancer.gov/clinical_trials/

Title: Phase II Study of Imatinib Mesylate in Patients With Philadelphia Chromosome Positive Chronic Phase Chronic Myelogenous Leukemia

Protocol Number: COG-AAML0123
Participating Institutions: Children’s Oncology Group
Contact: Judith Everett, (626) 447-0064, ext 116
Latest Information: http://www.cancer.gov/clinical_trials/

Title: Phase II Study of Imatinib Mesylate in Patients With Relapsed or Refractory Pediatric Solid Tumors

Protocol Number: COG-ADVL0122
Participating Institutions: Children’s Oncology Group
Contact: Judith Everett, (626) 447-0064, ext 116
Latest Information: http://www.cancer.gov/clinical_trials/

Title: Phase II Randomized Study of R115777 in Pediatric Patients With Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Protocol Number: NCI-01-C-0222A, NCI-T99-0090
Participating Institutions: National Cancer Institute Pediatric Oncology Branch
Contact: Brigitte C. Widemann, (301) 496-7387; for a complete listing of study contacts, click here
Latest Information: http://www.cancer.gov/clinical_trials/

Phase I/II

Title: A Phase I/II Trial of STI571 in Children With Newly Diagnosed Poor Prognosis Brainstem Gliomas and Recurrent Intracranial Malignant Gliomas
Protocol Number: PBTC-006
Participating Institutions: Pediatric Brain Tumor Consortium
Contact: Ian F. Pollack, (412) 692-5881

Phase I

Title: Phase I Study of R115777 in Pediatric Patients With Refractory Leukemia
Protocol Number: COG-ADVL0116, NCI-01-C-0196, NCI-1930
Participating Institutions: National Cancer Institute Pediatric Oncology Branch, Children’s Oncology Group
Contact: Brigitte C. Widemann, (301) 496-7387; for a complete listing of study contacts, click here
Latest Information: http://www.cancer.gov/clinical_trials/

Title: Phase I Study of PS-341 in Pediatric Patients With Advanced Solid Tumors
Protocol Number: COG-ADVL0015
Participating Institutions: Children’s Oncology Group
Contact: Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click here
Latest Information: http://www.cancer.gov/clinical_trials/

Title: Phase I Study of SCH 66336 in Children With Recurrent or Progressive Brain Tumors
Protocol Number: PBTC-003
Participating Institutions: Pediatric Brain Tumor Consortium
Contact: Mark W. Kieran, (617) 632-4907; for a complete listing of study contacts, click here
Latest Information: http://www.cancer.gov/clinical_trials/

Pilot Studies

Title: Phase II Pilot Study of Intensified Chemotherapy With or Without Allogeneic Hematopoietic Stem Cell Transplantation in Children With Very High-Risk Acute Lymphoblastic Leukemia
Protocol Number: COG-AALL0031
Participating Institutions: Children’s Oncology Group
Contact: Judith Everett, (626) 447-0064, ext 116
Latest Information: http://www.cancer.gov/clinical_trials/

Title: Intensive Induction Therapy for Children With Acute Lymphoblastic Leukemia Who Experience a Bone Marrow Relapse
Protocol Number: AALL01P2  
Participating Institutions: Children’s Oncology Group  
Contact: Judith Everett, (626) 447-0064, ext 116

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