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Pediatric Oncology

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Abstract

Intensive use of cytotoxic agents in multimodality therapeutic regimens has resulted in almost 80 percent 5-year disease-free survival, and cure in the majority of childhood cancer patients. However, such success has come at the expense of severe acute or delayed toxicities, and an increased occurrence of secondary cancers. With an increasing understanding of the genetic changes that underlie transformation in childhood cancer, rational approaches using agents that target these transforming events are being developed. Current and future strategies in developing tumor-selective therapy using inhibitors of signaling pathways dysregulated in leukemias (FLT3, NOTCH1) and solid/brain tumors (ErbB1-4, IGF-IR, PTCH1), and the challenges in developing less toxic, but equally effective treatments in pediatric oncology are presented.

Introduction

Since the 1960's survival rates for children with cancer have improved dramatically. The overall 5-year survival rate for children with cancer is approaching eighty percent [1]. In the United States the incidence of pediatric cancer is relatively low, about 12,400 new cases diagnosed annually in children and adolescents under 20 years of age. Thus, development of new therapies for children with cancer presents certain challenges unique to this population. The combination of low incidence and increasingly effective primary therapy results in relatively few children eligible for evaluating experimental therapies, and those that are available have generally been extensively treated and have highly resistant disease [2], hence may not be a good 'signal' population for identifying a drug that may have significant clinical activity at diagnosis.

In pediatric oncology the overall intent is to cure the child. The major advances in cures have been due to dose intensification of cytotoxic agents, and introduction of new agents (notably, cisplatin and etoposide). However, this has come at the expense of increased morbidity, and delayed toxicities (cardiomyopathy from doxorubicin) [3], or secondary tumors in patients treated with etoposide or 6-thioguanine [3,4]. It has to be acknowledged that further intensification of cytotoxic therapy is limited due to cumulative toxicity that frequently necessitates substituting new agents for other (perhaps equally effective) cytotoxic drugs. The other dilemma is that many 'molecular targeted' agents are essentially cytostatic, thus unlikely to eradicate disease. Thus, while stabilization of disease for several months in adult oncology with bevacizumab when added to 5-fluorouracil/leucovorin for treatment of colon cancer may be significant [5], such gain in survival is not particularly meaningful in context of pediatric oncology. One challenge to the field is to identify drug targets to which tumors have become dependent (so-called 'oncogene addiction') [6]. Such tumor-specific drug targets would be analogous to BCR/Abl in chronic myelogenous leukemia (CML) [7] or non-small

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cell lung cancers with activating mutations of the epidermal growth factor receptor (ErbB1) [8] where inhibitors such as imatinib mesylate or gefitinib, respectively, have cytoreductive effects. A second challenge will be to integrate these newer agents into curative therapy for childhood cancer, with the anticipation of reducing morbidity and long-term sequelae of current multimodality therapies.

Agents evaluated or currently being evaluated since 2001 in phase I or II clinical trials conducted through the Children's Oncology Group (COG) or the Pediatric Brain Tumor Consortium (PBTC) are shown in Table 1. These can be divided into receptor kinase or signaling inhibitors, agents that target DNA or histone modification, targeted toxins, antibodies, antiangiogenic agents, novel drugs that target apoptosis pathways, proteasome or molecular chaperones, and cytotoxic agents. The chemical structures for the non-biological agents are shown in Figure 1. Here we will focus largely on the signaling inhibitors under development, and how emerging molecular genetic information about pediatric cancers may help in directing therapies based on these characteristics to create what is termed 'molecularly targeted therapy'.

Signaling inhibitors

There are multiple clinical trials of signaling inhibitors that focus on ErbB family of receptors (erlotinib, gefitinib, lapatinib, trastuzumab) or multitargeted kinase inhibitors (sorefinib, dasatinib, sunitinib), some of which are based on biological characteristics of particular pediatric histiotypes, Table 2. For example, epidermal growth factor (EGF) is reported to be a mitogen for several brain tumor histiotypes, or there is association of increased receptor expression with poor prognosis in these tumors. Consequently, targeting ErbB1 is logical. However, whether these tumors are 'addicted' to this pathway is less clear. In non-small cell lung cancer (NSCLC) tumor regressions appear to associate with activating mutations of ErbB1 [8]. Similar data is not available for childhood brain tumors. This raises the question of whether inhibiting a single pathway represents a realistic therapeutic strategy. For example, tumor cells mutated for the lipid phosphatase PTEN, which occurs in childhood glioblastoma, appear resistant to ErbB1 inhibition, but in these cells inhibition of both Akt and ErbB1 signaling results in hypophosphorylation of the proapoptotic molecule Bad, and apoptosis [9]. In glioblastoma, for example, while EGF-signaling is reported to be dysregulated so are the IGF-I, PDGF, bFGF and HGF-SF signaling pathways (Table 2). Similarly, multiple growth factors appear to be mitogens for neuroblastoma, Ewing sarcoma and other tumors. Thus, for effective therapy aimed at curing a patient, it may be necessary to inhibit multiple pathways simultaneously. The concern is whether this will be possible without excessive toxicity. That multi-targeted kinase inhibitors appear to be tolerated, and in some adult malignancies such as renal cell carcinoma are active, would suggest that inhibiting several signaling pathways is a therapeutic option [10]. Identifying which pathways to inhibit in specific subsets of childhood tumors then becomes the challenge. A partial listing of agents reported to inhibit each of the signaling pathways is presented in Table 2.

An alternative approach is to identify critical 'nodal' kinases in signaling cascades that may be targeted. Both phosphatidylinositol 3' kinase (PI3K) and Akt/PKB represent kinases that are activated downstream of multiple growth factor receptors, and are the focus for drug development [11-14]. Akt inhibitors may be particularly effective in tumors with mutated PTEN such as childhood glioblastoma [15]. Perifosine, a putative Akt inhibitor [16,17] is in adult clinical trials. Rapamycin analogs, CCI-779 (temsirolimus) and RAD001 (everolimus), specific inhibitors of mTOR serine/threonine kinase downstream of Akt, have completed phase I clinical trials in children. In preclinical testing rapamycin has demonstrated broad-spectrum activity against childhood cancer models causing objective regressions in sarcomas and T-cell acute lymphoblastic leukemia (ALL) models.

Molecularly targeted therapy for leukemia

Several targets specific for certain leukemias have been identified. In acute promyelocytic leukemia (PML), rearrangement of the retinoic acid receptor- α , caused by the t(15:17) chromosomal translocation, inactivates the growth suppressing and differentiating activity of the retinoic acid receptor. The PML-RAR α fusion protein has the potential to mediate myeloid differentiation at pharmacological doses of its ligand (all *trans*-retinoic acid), which is dependent on the dissociation of the HDAC/co-repressor complex [18]. More recently, two signaling pathways activated in certain leukemias have been identified that also present therapeutic opportunities.

FLT3 Inhibitors

The FLT3 receptor and its ligand are expressed in many adult and childhood leukemias [19]. In addition, activating mutations of FLT3, caused by internal tandem duplications (ITD) that result in ligand-independent dimerization and receptor auto-phosphorylation [20,21], or activating mutations within the 'activation loop' [22,23] suggest a causal role of FLT3 in the pathogenesis of these leukemias. In childhood AML activating mutations occur in 8 percent of patients and 17 percent of infant ALL with MLL (for mixed-lineage leukemia or myeloid-lymphoid leukemia) rearrangements. ITD within the FLT3 receptor appear less frequent in childhood AML compared to adult disease, and is rare in childhood ALL [24,25]. Several FLT3 inhibitors are currently in clinical trials (Table 3). Preliminary clinical results indicate that CEP701-induced inhibition of FLT3 is associated with clinical activity in AML patients with FLT-activating mutations [26]. FLT3-ITD may require the molecular chaperone HSP90 for correct folding, consequently inhibitors of heat-shock protein 90 (HSP90) such as Herbinycin A and radicicol have been reported to have cytotoxic effects against cells expressing FLT3-ITD [27]. FLT3 expressing cells are also selectively sensitive to HSP90 inhibitors, with or without addition of FLT3 inhibitors [28]. The geldanamycin derivative 17-allylamino-17-demethoxygeldanamycin (17-AAG; Table 1) appears to synergize *in vitro* with FLT3 inhibitors inducing cell death [29]. Clearly, evaluation of such combinations in clinical trials for FLT3-driven AML will be of intense interest.

γ -Secretase inhibitors

A second area of intense drug development is in T cell acute lymphoblastic leukemia (T-ALL). Most human T-ALLs have activating mutations that involve the extracellular heterodimerization domain and/or the C-terminal PEST domain of NOTCH1 [30]. Physiologic activation of NOTCH1 receptors occurs when ligands of the Delta-Serrate-Lag2 (DSL) family bind the extracellular domain and initiate a series of proteolytic cleavages. The final cleavage is catalyzed by γ -secretase to generate intracellular NOTCH (ICN) which translocates to the nucleus. As part of a large transcription complex ICN is required for commitment of pluripotent progenitors to the T cell lineage [31]. Both β and γ -secretases are proteases that cleave amyloid precursor protein, hence have been targets for drug development for Alzheimers patients. Inhibition of γ -secretase in T-ALL cell lines results in cytostasis (cells block in G1 phase of the cell cycle) [30] and in Kaposi sarcoma cells treatment is associated with apoptosis [32]. One complication with inhibitors of γ -secretase is marked effects on lymphocyte development and on the intestine manifest as decreased overall thymic cellularity and impaired intrathymic differentiation at the CD4⁻CD8⁻CD44⁺CD25⁺ precursor stage. Treatment also increases goblet cell number and drastically alters tissue morphology [33]. These effects are reversible after drug discontinuation, however, it raises the concern that severe side effects could prevent this from being effective therapy for T-ALL.

Molecularly targeted therapy for solid tumors

While the dramatic effects of imatinib in adult gastrointestinal stromal tumors (GIST) represent a new paradigm in anticancer therapy for solid tumors, such pivotal targets for childhood solid tumors and brain tumors have not yet been identified. Many childhood solid tumors are associated with chromosomal translocations that result in chimeric genes encoding fusion proteins, many of which are transcription factors. For sarcomas, similar translocations are common to both childhood and adult tumors, Table 4. While transcription factors, *per se*, may not provide robust drug targets, potentially pathways they activate or suppress will. For example, alveolar rhabdomyosarcoma (ARMS) is associated with t(2;13)(q35;q14) or t(1;13)(q36;q14) translocations which generate PAX3-FKHR or PAX7-FKHR fusion products, respectively. These chimeric transcription factors enhance activation of PAX3 and PAX3-FKHR target genes that include anti-apoptotic Bcl-xL, and suppress the function of undisrupted FKHR, leading to increased expression of TGF α , FLT1, PDGF α , and IGF-1 receptors. In synovial sarcoma the SYT-SSX fusion protein that results from the X,18 translocation results in overexpression of Bcl-2, EGFR (ErbB1) and ErbB2 [34]. Thus, for both synovial sarcoma and ARMS, inhibition of Bcl-family members using either antisense (Genasense, Table 1), or BH3 mimetic drugs [35,36] such as ABT-737 or ABT-263 in combination with cytotoxic agents has considerable rationale. Inhibition of ErbB receptors with lapatinib, or the pan-ErbB inhibitor ARRY-334543 may be effective cytostatic treatment for synovial sarcoma [34]. Similarly, inhibiting ErbB-family receptors may prove to be a useful therapeutic approach to treatment of medulloblastoma where Erb2 and Erb4 is overexpressed [37], and expression of NRG-1 β (neuregulin-1 β) that binds to te Erb2/Erb4 heterodimer, occurs in most tumor samples.

IGF-I receptor inhibitors

Dysregulated IGF-IR signaling appears to be common to many childhood solid tumors. In addition to ARMS, most embryonal rhabdomyosarcomas (ERMS) have allelic loss at chr 11p15.5. This is a region of IGF-2 gene that is overexpressed in both ARMS and ERMS. The IGF-2 gene normally is imprinted from maternal allele, but in ERMS it becomes transcriptionally active, and activation of IGF-2 locus may be primary genetic event in the ERMS. IGF-I is also a mitogen for osteosarcoma [38], and IGF-IR is a mediator of autocrine growth in Ewing sarcoma. Dysregulated IGF-I signaling is common to several adult malignancies, hence IGF-IR has become a major focus for therapeutic development [39-45] with four fully human antibodies in adult phase-I or -II clinical trials. These agents show specificity for the IGF-IR although they may inhibit chimeric receptors formed through heterodimerization with the insulin receptor. In preclinical models of childhood cancers, antibody mediated down regulation of IGF-IR significantly retards growth of many tumors, and induces regressions in several sarcoma histiotypes. Molecular characterization of these sensitive models where IGF-IR signaling appears to be critical could identify subsets of tumors that have become 'addicted' to this pathway. In other preclinical models blocking IGF-IR signaling results in significant retardation of tumor growth although in a clinical setting this response would be scored as progressive disease. In these models with intermediate sensitivity combinations of signaling inhibitors would potentially be more effective antitumor therapy.

Several classes of small molecule inhibitors of IGF-IR have been described, including tyrphostins, pyrrolopyrimidines [46,47], substituted benzimidazole derivatives [48] and diarylureas [49]. In contrast to antibodies directed at IGF-IR, small molecule ATP-competitive IGF-IR inhibitors do not induce downregulation of the receptor, and in most cases do not discriminate between the insulin receptor and the IGF-IR [48,50]. As a consequence, these inhibitors may have more pronounced effects on glucose homeostasis (causing hyperglycemia and hyperinsulinemia). Several small molecule inhibitors of IGF-IR may be close to clinical trial.

mTOR inhibitors

Rapamycin and its analogs specifically inhibit the serine/threonine kinase mTOR, and inhibit cap-dependent translation [51]. Notably, inhibition of mTOR leads to decreased levels of cyclin D1, ornithine decarboxylase, IGF-II, c-MYC, and VEGF, potential drug targets in many childhood cancers. For example, more than 85 percent of Ewing sarcoma family tumors are characterized by a specific translocation between chromosomes 11 and 22, t(11;22)(q24;q12) that results in FLI-EWS fusion product. EWS-FLI-1 protein binds to the *c-myc* promoter, which probably accounts for the elevated levels of c-MYC observed in Ewing's sarcoma [52]. In medulloblastoma the *c-myc* locus (8q24) is amplified in about 10 percent of cases and c-myc mRNA overexpression in 42 percent. Consequently, one may anticipate agents that block *c-myc* translation, such as rapamycin [53], may have significant effect in these tumors. Combination of rapamycin analogs with inhibitors of IGF-IR would appear to be rational for treatment of sarcomas and certain leukemias based on the preclinical data.

Inhibitors of Smoothed

Mutations of the Sonic Hedgehog (Shh) receptor Patched-1 (PTCH1) gene underlie the human developmental disorder Gorlin syndrome or nevoid basal cell carcinoma syndrome. One to two percent of patients developing medulloblastoma have these syndromes, and heterozygous loss of PTCH1 occurs in approximately 10 percent of sporadic medulloblastoma [54,55]. Shh binds PTCH1 and derepresses Smoothed (SMO) leading to increased expression of the transcription factor GLI. Inactivating mutations in PTCH1 lead to aberrant expression of GLI [56]. Cyclopamine has been shown to suppress the response of target tissues to Shh by binding to SMO [57], although with relatively low affinity. More recently, several small molecule inhibitors have been identified. One of these, a benzimidazole derivative, Hh-Antag691 blocked the function of Smo in mice with *ptch1*^{-/+} medulloblastoma [58]. Other small molecule inhibitors of Smo are under development such as CUR61414 [59].

Cyclin-dependent kinase inhibitors

Common to many childhood cancers are amplifications or overexpression of genes encoding cyclin dependent kinases, CDK4/6, or loss of inhibitors of these CDKs. Inhibition of CDK4 by stabilization of p27^{Kip1} is associated with differentiation of neuroblastoma cells, and tight G1 arrest [60]. Similarly, inhibition of CDK4/6 with PD332991 leads to increased myogenic differentiation and G1 cell cycle arrest of rhabdomyosarcoma cells [61]. Thus, potentially CDK4/6 inhibitors could be part of a differentiation-inducing therapy, similar to retinoic acid, particularly in the setting of minimal residual disease. Amplification of MYCN in neuroblastoma and some sarcomas may also be a relevant target [62]. Recently it was shown that the stability of MYCN protein is dependent on Akt phosphorylation and suppression of GSK3 β [63]. Inhibition of PI3K, upstream of Akt, led to rapid decreases in MYCN protein, and tumor growth inhibition. Inhibitors of PI3K [12], Akt [13,14], and GSK3 β [64] are under development, hence may have application for treating tumors with MYCN amplification. However, whether these agents will have adequate therapeutic utility relative to potential effects on glucose homeostasis remains a concern. As Akt is a client protein for the molecular chaperone HSP90, potentially inhibitors of HSP90, such as 17-AAG (Table 1, novel agents) may also reduce Akt signaling to MYCN.

Conclusions

As in adult cancer, drug development in pediatric cancer is undergoing a paradigm change. While cytotoxic agents still form the basis for curative therapy, there is increasing focus on targeting the consequences of specific genetic lesions causal for the malignant phenotype. Through the use of RNA interference a better understanding of the consequences of chimeric transcription factors is emerging that may identify tumor-selective targets. However, for most

tumors targeting a specific pathway, or receptor, may retard growth but not induce cell death. Consequently, the challenge will be to identify the second target that induces cell death only in the context of the first lesion (so-called synthetic lethality), and ultimately to identify those targets prospectively and tailor therapy accordingly. The other challenge will be to integrate molecularly targeted agents, signaling inhibitors, histone deacetylase inhibitors, or antiangiogenic agents that target stromal components of tumors, with current intensive chemotherapy regimens without increasing toxicity, or reducing efficacy.

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Figure 1.

Table 1

Phase I/II drugs in development: Protocols activated between 2001-2007.

Agent	Phase	Indication/population	Mechanism/Target
Receptor/ tyrosine kinase/signaling inhibitors			
Imatinib (Gleevec)	Pilot	Very high risk ALL	BCR/ABL inhibitor
	II	Chronic Phase CML	BCR/ABL inhibitor
	I/II	Newly diagnosed poor prognosis brainstem gliomas/ Recurrent intracranial malignant gliomas	BCR/ABL, c-Kit
Tarceva (OSI-774)	I	Recurrent/Refractory solid tumors including brain tumors	ErbB1 inhibitor
Lapatinib	II	Recurrent/progressive medulloblastoma/glioblastoma/ependymoma	ErbB1/2
Gefitinib (Iressa)	I/II	Brain stem tumors/incompletely resected supratentorial malignant gliomas (+ XRT)	ErbB1
Trastuzumab (Herceptin)	II	Metastatic Osteosarcoma overexpressing HER-2 (antibody)	ErbB2 inhibitor
Sunitinib	I	Refractory solid tumors	Multi-targeted kinase inhibitor
Sorafenib (BAY-43-9006)	I	Refractory solid tumors	Multi-targeted kinase inhibitor
Dasatinib (BMS-354825)	I	Recurrent/Refractory solid tumors Ph+ Leukemia	Src/other kinases
Tipifarnib (R115777)	I/II	Non-disseminated intrinsic diffuse brainstem gliomas (+ XRT)	Farnesyltransferase inhibitor (Ras?)
DNA methylation/histone deacetylation inhibitors			
Decitabine (DAC)	I	Recurrent/Refractory ALL	DNA methyltransferases
Depsipeptide	I	Recurrent/Refractory solid tumors and leukemias	HDAC inhibitor
SAHA	I	Recurrent/Refractory solid tumors	HDAC inhibitor
Valproic acid	I	Refractory solid tumors/CNS tumors	HDAC inhibitor
Targeted Toxins			
IL13-PE38QQR	I/II	Recurrent malignant glioma	Targeted-Pseudomonas toxin
TGF-TP38	I/II	Recurrent/progressive supratentorial high-grade gliomas	TGF α -targeted-Pseudomonas toxin
Campath-1H Alemtuzumab	II	ALL ($\geq$ Second relapse/ or 2 induction failures)	Humanized antibody against CD52
Epratuzumab	II	Relapsed CD22-Positive ALL	Humanized antibody: immune-based therapy
Hu14.18-IL2 (EMD 273063)		Refractory Neuroblastoma	Immune activator
Anti-angiogenic agents			
Bevacizumab (Avastin)	I	Recurrent/Refractory solid tumors	VEGF
Lenalidomide (CC-5013)	I	Recurrent/progressive primary brain tumors	Antiangiogenic
	I	Refractory solid tumors/myelodysplastic syndrome	Anti-angiogenic
AZD2171	I	Recurrent/Refractory CNS tumors	VEGFR1-3 c-Kit
Cilengitide (EMD 121974)	I	Recurrent/progressive brain tumors	Antiangiogenic
Novel Targets			
G3139 (Genasense)	I	Recurrent/Refractory solid tumors (with cytotoxic therapy)	BCL-2 antisense
17-AAG	I	Recurrent/Refractory solid tumors or leukemia	HSP90 inhibitor
Velcade (PS-341)	II	Refractory/Recurrent Hodgkins Disease	Proteasome
	I	Recurrent/Refractory leukemias	
Cytotoxic Agents			
ABT-751	II	Relapsed/Refractory Neuroblastoma	Tubulin/antimitotic
Ixabepilone (BMS247550)	II	Refractory solid tumors	Tubulin/antimitotic
Ispinesib (SB-715992)	I	Refractory solid tumors	Kinesin inhibitor/antimitotic
Hycamtin (topotecan)	I	Intrathecal/neoplastic meningitis	DNA topoisomerase I
Irinotecan	II	Refractory solid tumors	DNA topoisomerase I
Cloretazine	I	Recurrent/progressive primary brain tumors	DNA alkylating

Agent	Phase	Indication/population	Mechanism/Target agent
Temozolomide	I	Recurrent/refractory leukemias	DNA methylator
Temozolomide	II	High Grade Glioma, Diffuse Intrinsic Pontine Gliomas	DNA methylator
O6-Benzylguanine	II	Recurrent/progressive high-grade GBM /brainstem tumors (+ temozolomide)	MGMT (modulator)
Pemetrexed (Alimta)	I	Recurrent/Refractory solid tumors	Antifolate

Table 2
Dysregulated growth factor pathways in pediatric cancers

Growth factor	Tumor type	Specific tumor	Inhibitors under development
EGF	CNS tumors SNS tumors Primary liver tumors Renal tumors	Glioblastoma (EGFR) Ependymoma (ErbB-2/4) Medulloblastoma (ErbB-2) Neuroblastoma (ErbB-2) Hepatocellular carcinoma Wilms' tumor	<u>Anti-EGFR (ErbB1)</u> ABX-EGF BMS 599626 Cetuximab EKB-569 EMD 72000 Gefitinib Lapatinib ICR-62 IMC-225 Erlotinib; PD 153035 PKI-166 TP-38 <u>Anti ErbB receptors:</u> ARRY334543 BMS 599626 CI-1033, CP-724714 MP-412 PD 168939 Trastuzumab
PDGF	CNS tumors STS Bone tumors Renal tumors	Glioblastoma Ewing's sarcoma (PDGF- β) Gastrointestinal tumors (PDGFR- α , c-kit) Osteosarcoma Wilms' tumor	AG 1295, AG1296 AG 17 AG 370 AGL 2033, AGL 2043 CT52923 JNJ-10198409 Phenylbenzimidazoles Pyridinyl quinoline RPR101511A SU 101 SU 6668 SU 11248
IGF-I	CNS tumors SNS tumors STS Renal tumors Primary liver tumors	Glioblastoma Medulloblastoma Neuroblastoma Ewing's sarcoma Wilms' tumor (IGF-IR) Hepatocellular carcinoma	AG 538 BMS-536924 BMS-554417 Cyclolignan PPP C100 I-OMeAG
IGF-II	Primary liver tumors SNS tumors STS	Hepatocellular carcinoma Neuroblastoma Rhabdomyosarcoma	JB-1 NVP-ADW742 NVP-AEW541 Pegvisomant, Antibodies: CP751871 IMC A12 F50035 19D12 R1507
bFGF	CNS tumors SNS tumors STS Bone tumors	Glioblastoma Neuroblastoma (FGFR1) Ewing's sarcoma Embryonal rhabdomyosarcoma Osteosarcoma	CHIR-258 (<i>anti FGFR3</i>) SU 5402 SU 6668 SU 11657
VEGF	STS Renal cancers	Gastrointestinal tumor Rhabdomyosarcoma Wilms' tumor	AAL 881 AEE 788 AG 13925 AG 013736 AMG 706 AZD 2171 Sorafenib Bevacizumab BMS-582664 CEP-7055 CP-547632 GFA-116 GW 786024 IMC-1121B KRN 951 PTK 787/ZK222584 SU 5416 SU 6668
	SNS tumors	Neuroblastoma	
	Bone tumors	Osteosarcoma Ewing sarcoma	

Growth factor	Tumor type	Specific tumor	Inhibitors under development
			SU 11248 SU 11657 ZD 6474
HGF-SF	CNS tumors SNS tumors STS Primary liver tumors Bone tumors	Glioblastoma Neuroblastoma Rhabdomyosarcoma Synovial sarcoma Hepatocellular carcinoma Osteosarcoma	PHA-665752 SU 5416 XL880

SNS, sympathetic nervous system; STS, soft tissue sarcoma

Table 3

FLT3 inhibitors in clinical evaluation

Inhibitor	FLT3 K _i (nM)	Other RTK targets
CEP 701	3	TrkA, VEGFR2
PKC 412	10	PKC
CT 53518 (MLN18)	10-220	PDGFR, KIT
SU5614	100	KIT, VEGFR2
SU 11248		VEGFR2, PDGFR, KIT

Table 4**Chromosomal translocation in sarcoma**

Histology	Chromosomal aberrations	Genes involved
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(q36;q14)	Pax3/FKHR Pax7/FKHR
Ewing sarcoma	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12)	FLI/EWS EWS/EGR EWS-ETV1
Dermatofibrosarcoma	t(17;22)(q22;q13)	COL1A1-PDGFB
Infantile fibrosarcoma	t(12;15);+11; also +8,+17,+20	ETVG(TEL)/NTRK3
Neurofibrosarcoma	Deletion 17q11.2	
Malignant fibrous histiocytoma	19p+, ring chromosome	
Hemangiopericytoma	t(12;19)(q13;q13.3) and t(13;22)(q22;q13.3)	
Alveolar soft part sarcoma	t(x;17)(p11.2;q25)	ASPL/TFE3
Leiomyosarcoma	t(12;14)	
Synovial sarcoma	t(x;18)(p11.2;q11.2)	SYT/SSX
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	EWS-CHN
Clear cell sarcoma (MMSP)	t(12;22)(q13;q12)	ATF1/EWS
Myxoid liposarcoma	t(12;16)(q13;p11)	FUS/CHOP
Desmoplastic tumors	t(11;22) (p13;q12)	WT1/EWS