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Histone deacetylase inhibitors in cancer therapy

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Abstract

Purpose of review—The purpose of this review is to provide an overview of recent advances in the development of histone deacetylase inhibitors (HDACi) for the treatment of cancer.

Recent findings—Recently, there has been a dramatic expansion of HDACi clinical investigation. There are now 11 HDACi in clinical trial, including inhibitors with a broad spectrum of HDAC isoform inhibitory activity as well as drugs with isoform selectivity. Over 70 combination therapy trials are in progress. Major areas of progress covered include the entry of new HDAC inhibitors into clinical development, recent progress in understanding of molecular mechanisms of HDACi anticancer activity, and a preclinical and clinical update on HDACi in combination.

Summary—In the period under review there have been advances in understanding of HDACi mechanisms of action, identification of rational combinations that address increased efficacy and overcoming resistance, and greatly expanded clinical development of pan-HDAC-inhibitory and isoform-selective inhibitors in monotherapy and combination therapy protocols.

Keywords

cancer therapy; clinical trial; combination therapy; histone deacetylase inhibitors

Introduction

Chromatin-templated activities including DNA transcription, replication, and repair are regulated by a variety of posttranslational modifications, among which histone acetylation plays a prominent role. Numerous nonhistone proteins are histone deacetylase (HDAC) substrates, including many of the most critical regulators of the malignant phenotype. Reciprocal acetylation/deacetylation has been shown to have profound effects on protein function, such as the recent demonstration that acetylation is absolutely required for p53 activation [1•], and small molecule HDAC inhibitors have shown promising anticancer activity preclinically and clinically [2–11].

Despite the central importance of HDAC substrates in the biology of cancer cells, at clinically achievable concentrations histone deacetylase inhibitors (HDACi) are rarely cytotoxic as single agents. Thus, from the onset of their development as oncology drugs, it has been commonly assumed that HDACi would ultimately be used in combination. As

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described here, in the past year progress has been made in moving toward the goal of effective combination therapy. There are now 11 HDACi in clinical trial, seven of which are undergoing testing in combination protocols. In addition to highlighting publications on monotherapy and combination therapy, we discuss advances in HDACi basic mechanisms of activity, HDACi pharmacodynamic assay development, and the impact of HDACi on systems level biological activities including angiogenesis, metabolism, and immune response. This article covers the time period from January 2007 to June 2008. Only a small fraction of preclinical and clinical articles published during this time period can be mentioned. The aim of this overview is to highlight major new findings and ideas related to the development of HDACi for the treatment of cancer.

Update on histone deacetylase inhibitors in clinical development

On 6 October 2006 the US Food and Drug Administration (USFDA) granted regular approval to vorinostat for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients with progressive, persistent, or recurrent disease on or following two systemic therapies. The pivotal study supporting approval was an open-label, single-arm, multicenter phase IIB trial of 74 patients with CTCL who had previously failed at least two prior systemic therapies, one of which must have contained bexarotene [12••]. There was a 30% objective response rate with a median response duration of 168 days in a heavily pretreated advanced CTCL patient population. In a supportive phase II single-institution trial of 33 CTCL patients there was a 31% response rate [13••].

In June 2008 Gloucester Pharmaceuticals (Cambridge, Massachusetts, USA) announced that a phase IIB registration trial of romidepsin in CTCL was completed and that the trial met its primary endpoint based on overall response rate. Gloucester Pharmaceuticals plans to submit a new drug application to the USFDA later in 2008 (http://www.gloucesterpharma.com/press/releases/pr060508.html).

New HDACi in clinical development include the hydroxamates CRA-024781 from Celera Genomics (South San Francisco, California, USA), ITF2357 from Italfarmaco (Milan, Italy), SB939 from S*BIO Pte Ltd (Singapore), and R306465 from Johnson & Johnson (Beerse, Belgium) (see Table 1 [14–17] for additional HDACi information). Novartis Pharmaceuticals (East Hanover, New Jersey, USA), which had two hydroxamate HDACi in clinical development, LAQ824 and LBH589 (panobinostat), has chosen to focus on development of panobinostat.

Interest in isoform-selective HDACi continues. The effects of the pan-HDACi hydroxamic acid derivatives are being compared with more isoform-selective compounds such as the benzamides SNDX-275 and MGCD0103 and the cyclic peptide romidepsin. In addition there is increasing interest in the class II enzyme HDAC6, which has been implicated in tumor cell motility and metastasis, in deacetylation of the molecular chaperone heat shock protein 90 (Hsp90), and in the regulation of tumor cell death via autophagy [18,19•]. The HDAC6 inhibitor tubacin has been a valuable probe of HDAC6 function [20], and novel small molecule inhibitors of HDAC6 have been synthesized that extend understanding of the structural requirements for selective HDAC6 inhibition [21].

Preclinical studies

Preclinical research in areas of particular interest published during the review period is summarized below.

Autophagy, the proteasome and apoptosis

Eukaryotic cells primarily use two regulated processes for large-scale catabolism, autophagy, and apoptosis. Recently, there has been intense interest in both processes as drug targets, and a variety of studies have demonstrated synergy of HDACi with autophagy and proteasome inhibitors.

Treatment with vorinostat induces both apoptosis and autophagy. To examine a potential role of autophagy in vorinostat resistance Carew *et al.* [22•] tested the effect of vorinostat on imatinib-resistant chronic myelogenous leukemia (CML), in the presence and absence of the autophagy inhibitor chloroquine. Chloroquine dramatically augmented the anticancer activity of vorinostat in CML cell lines and primary cells. Generation of reactive oxygen species (ROS) is a critical event in vorinostat-induced cell death, and chloroquine, which induces ROS in other systems, markedly augmented vorinostat-induced superoxide generation.

Dai *et al.* [23] in chronic lymphocytic leukemia cells and Duan *et al.* [24] in head and neck squamous cell carcinomas demonstrated that HDACi enhance nuclear factor-kappa B (NF-κB) activation resulting in HDACi resistance, and that this activation is inhibited by bortezomib. NPI-0052 (Nereus Pharmaceuticals, San Diego, California, USA), a second-generation proteasome inhibitor that unlike bortezomib, irreversibly binds to the 20S proteasome and inhibits all three proteasome catalytic activities, has entered clinical trial in refractory solid tumors and lymphoma. Miller *et al.* [25•] investigated the effect of combining SNDX-275 and valproic acid (VPA) with NPI-0052 in leukemia cells *in vitro* and reported synergistic apoptosis associated with superadditive increases in ROS, consistent with a role for oxidative challenge in the observed synergy.

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) preferentially induces apoptosis in malignant cells. However, many cancers are resistant to TRAIL treatment. Various HDACi have been shown to synergize with TRAIL in inducing tumor cell death [26]. Lexatumumab (Human Genome Sciences, Rockville, Maryland, USA) is an agonistic monoclonal antibody to TRAIL-R2. Nawrocki *et al.* [27] demonstrated that vorinostat and trichostatin A (TSA) reduced lexatumumab resistance in colon cancer cells via induction of p21 expression, p21-dependent inhibition of cdc2, and subsequent instability and loss of expression of the antiapoptotic protein survivin.

Zhao *et al.* [28] demonstrated that apoptosis induced by the anti-CD20 antibody rituximab (Rituxan, Biogen Idec/Genentech, Cambridge, Massachusetts/San Francisco, California, USA), used in the treatment of B-cell non-Hodgkin's lymphoma (NHL), is significantly enhanced by combination with vorinostat *in vitro* and in a lymphoma mouse model *in vivo,* in association with NF-κB inactivation and c-myc degradation.

Histone deacetylase inhibitors, translational inhibition, and heat shock protein 90 regulated proteolysis

In mantle cell lymphoma cells constitutively overexpressing cyclin D1, Kawamata *et al.* [29] demonstrated that vorinostat markedly downregulates cyclin D1 protein while having little effect on cyclin D1 gene expression or protein stability, and that the mechanism of downregulation is via inhibition of the PI3 kinase/Akt/mTOR/eIF4E-BP pathway, resulting in inhibition of cyclin D1 translation.

Acetylation of Hsp90 promotes proteasomal degradation of client proteins. Epidermal growth factor receptors (EGFRs) with activating mutations are dependent on Hsp90 for stability and function. Edwards *et al.* [30] showed that LBH589 induces Hsp90 acetylation and EGFR degradation in lung cancer cells with mutant EGFR, and that LBH589 and the EGFR tyrosine kinase inhibitor (TKI) erlotinib synergized in promoting apoptosis of nonsmall cell lung cancer (NSCLC) cells harboring EGFR mutations.

HDACs and DNA methyltransferase 1 (DNMT1) cooperate in epigenetic gene regulation. As shown by Zhou *et al.* [31•] DNMT1 forms a molecular chaperone complex with Hsp90, and LBH589 induces Hsp90 acetylation and DNMT1 degradation.

Histone deacetylase inhibitors, mammalian target of rapamycin inhibitors and angiogenesis

HDACi have been reported to inhibit angiogenesis through a variety of mechanisms, including HIF-1α downregulation and decreased expression of VEGF and other proangiogenic HIF-1α target genes. The mammalian target of rapamycin (mTOR) signaling pathway regulates angiogenesis as well as tumor survival and proliferation. Resistance to mTOR inhibitors has been associated with Akt phosphorylation and activation of survival mechanisms. Verheul *et al.* [32] tested the combination of LBH589 and the mTOR inhibitor rapamycin and reported that the combination abrogated constitutive and rapamycin-induced Akt phosphorylation, suppressed HIF-1α, and inhibited in-vivo tumor growth and angiogenesis.

Histone deacetylase inhibitors and nuclear receptor-targeted agents

Bigaku *et al.* [33] demonstrated potentiation of tamoxifen by HDACi in breast cancer cell lines, which was associated with downregulation of estrogen receptor and progesterone receptor protein and nuclear signaling. Fiskus *et al.* [34] reported that in estrogen receptorpositive breast cancer cells hydroxamic acid HDACi induced acetylation of Hsp90 and degradation of estrogen receptor-α with consequent attenuation of estrogen receptor signaling. Hsp90 acetylation was also associated with degradation of client proteins Her-2, phospho-ERK1/2, and phospho-Akt, which have been associated with intrinsic and acquired resistance to tamoxifen.

Progression of prostate cancer patients on hormonal therapy is thought to represent continued signaling of androgen receptor (AR) in the presence of low levels of androgen due to AR upregulation or activation [35]. Thus, agents that reduce AR expression or function are good candidates for therapy of castration-resistant prostate cancer. Marrocco *et al.* [36]

demonstrated that vorinostat decreased AR mRNA and protein, inhibited androgen signaling, and acted synergistically with the antiandrogen bicalutamide to induce apoptosis in prostate cancer cells.

HDACi have been shown to reverse epigenetic repression of the tumor suppressor retinoic acid receptor beta (RARb) [37]. Kato *et al.* [38] demonstrated LAQ824 induced RARb expression and restored retinoid sensitivity in retinoic acid-resistant melanoma cell lines.

Reversal of epithelial-mesenchymal transition by histone deacetylase inhibitors

Epithelial-mesenchymal transition (EMT) is a process that occurs normally during embryonic development and is thought to play a critical role in tumor progression by promoting invasiveness and metastasis [39]. EMT has been associated with resistance to targeted TKI therapy. Both EMT and TKI resistance have been reported to be reversible by HDACi [40]. Transforming growth factor beta 1 (TGF-β1), when it is aberrantly expressed in the tumor microenvironment, is an important inducer of EMT. Shan *et al.* [41] studied the mechanism of TGF-β1-induced EMT in lung adenocarcinoma cells *in vitro* and reported that HDAC6 is a critical regulator of EMT and, thus, a therapeutic target in pathological EMT.

Histone deacetylase inhibitors, Wnt signaling and cancer stem cells

An area of considerable importance in anticancer therapeutics is the identification and targeting of cancer stem cells. Although much needs to be learned about cancer stem cell signaling, there is a documented role for the Wnt/β-catenin pathway in cancer stem/progenitor cell biology [42]. Jiang *et al.* [43•] reported that *DACT3,* which is transcriptionally repressed in colorectal cancer, profoundly suppresses Wnt/β-catenin signaling, and that *DACT3* expression is repressed not by DNA methylation but by bivalent activating and repressive histone methylation marks at the *DACT3* promoter. They observed pharmacological reactivation of *DACT3* expression with the combination of TSA and the *S*-adenosylhomocysteine hydrolase inhibitor 3-deazaneplanocin A, and this combination induced dramatic apoptosis associated with inhibition of Wnt/β-catenin signaling. Their data demonstrating that *DACT3* is a therapeutic target of histone modifications have implications for colorectal cancer treatment and potentially, for targeting of cancer stem/progenitor cells driven by Wnt/β-catenin signaling.

Molecular basis of histone deacetylase inhibitor efficacy and resistance

Fantin *et al.* [44] identified constitutive signal transducers and activators of transcription (STAT) activation as a biomarker predictive of resistance to vorinostat in patients with CTCL. Nuclear STAT1 and nuclear phosphotyrosine-STAT3 in CTCL patient skin biopsies correlated with lack of clinical response to vorinostat. The pan-Janus-activated kinase inhibitor JAK-I, used to block the JAK/STAT pathway, was synergistic with vorinostat in antiproliferative effect in CTCL cells *in vitro.* Epping *et al.* [45•] performed a functional genetic screen to identify HDACi targets and determined that retinoic acid signaling is a rate-limiting target determining HDACi therapeutic efficacy. Using the Eμ-myc transgenic mouse model of B-cell lymphoma to examine the molecular basis of vorinostat efficacy and resistance, Lindemann *et al.* [46] reported that overexpression of the antiapoptotic proteins

Bcl-2 or Bcl-X_L or deletion of the proapoptotic BH3-only proteins Bim and Bid resulted in resistance to vorinostat therapy.

Histone deacetylase inhibitors as radiation sensitizers

A number of investigators have established that HDACi act as radiation sensitizers and prolong the expression of gH2AX, consistent with inhibition of DNA double-strand break repair [47]. HDAC3 is a critical component of the N-CoR/SMRT corepressor complex, which is aberrantly recruited by mutant transcription factors. Bhaskara *et al.* [48] used a conditional knockout of *Hdac3* to demonstrate that in interphase cells inactivation of HDAC3 results in apoptosis, preceded by DNA damage associated with defective DNA double-strand break repair. In contrast, quiescent *Hdac3*$^{-/-}$ mouse embryo fibroblasts were protected from DNA damage. Their data suggest that inhibition of HDAC3 results in DNA damage, impedes efficient DNA repair, and induces apoptosis with selectivity for cycling cells.

Histone deacetylase inhibitor effects on immune response

HDACi impact the immune system through a variety of mechanisms, including upregulation of tumor immune genes resulting in increased cytotoxic T-lymphocyte recognition, upregulation of major histocompatibility complex class I, class II and costimulatory molecules leading to increased CD4 and CD8 T-cell activation, induction of NKG2D ligand expression on tumor cells rendering tumor cells more sensitive to NK cytolysis, and upregulation of molecules including TAP1 and LMP2 that play a role in antigen processing and presentation [49,50]. In an examination of the role of LAQ824 in immunity, Brogdon *et al.* [51•] reported LAQ824 inhibited dendritic cell-regulated T helper 1 (Th1) effector and not Th2 effector cell activation and migration, and thus can alter the Th1 and Th2 balance in therapeutic settings. Using an immunocompetent orthotopic murine renal cell carcinoma model Kato *et al.* [52•] demonstrated synergistic antitumor activity of interleukin 2 and SNDX-275, accompanied by a decrease in immunosuppressive Foxp3$^+$ regulatory T cells and evidence of enhanced splenocyte antitumor cytotoxicity.

Histone deacetylases and metabolism

Using a postnatal liver-specific mouse knockout model, to understand HDAC3 function, Knutson *et al.* [53] demonstrated that loss of HDAC3 disrupts metabolic transcriptional networks and results in significant imbalances in carbohydrate and lipid metabolism. Chung *et al.* [54] used ^{31}P magnetic resonance spectroscopy to monitor tumor phospholipid metabolism in xenograft studies of the response to the pan-HDACi LAQ824. They report a correlation between increased phosphomonoester/total phosphorus ratio and tumor response, demonstrating HDACi-induced alterations in phospholipid metabolism and tumor bioenergetics.

Pharmacodynamic assay development

The great majority of HDACi pharmacodynamic studies have been an assessment of histone H3 and H4 acetylation in peripheral blood mononuclear cells. Although concentration-dependent modulation of this marker is frequently seen, this is rarely correlated with clinical

benefit. A greater emphasis is now being placed on obtaining tumor cells, including tumor biopsies and circulating epithelial tumor cells, and in identifying noninvasive techniques that measure drug activity against tumor.

Using multiparameter flow cytometric analysis [55] of bone marrow aspirates from acute myeloid leukemia (AML) patients in a phase I trial of SNDX-275, Gojo *et al.* [56] demonstrated quantification of hyperacetylation in blast cells versus normal marrow elements and correlation of tumor cell hyperacetylation with apoptosis and with p21 expression on a single cell level. Kummar *et al.* [57] used this assay to quantify hyperacetylation in different cell lineages in an SNDX-275 phase I trial in solid tumor and lymphoma patients. A new assay of HDAC enzymatic activity in intact cells using a cell-permeant substrate with a fluorescent read-out has been developed and tested in clinical trials of MGCD0103 [58,59]. In a phase I study of belinostat Steele *et al.* [60] demonstrated that patients with stable disease, and not progressive disease, showed a significant increase in plasma M30 epitope, the product of caspase-dependent cleavage of cytokeratin-18, which is thought to represent apoptosis of epithelial tumor cells.

Update on histone deacetylase inhibitor clinical trials

HDACi clinical trials and American Society of Clinical Oncology (ASCO) annual meeting abstracts are summarized in Table 2 [61 –112,113•,114–117,118•,119]. Some of the published trials are highlighted below. In HDACi monotherapy trials the majority of objective responses have been reported in CTCL and, to a lesser extent, other hematological malignancies. Only occasional objective responses have been reported in solid tumor monotherapy trials. Encouragingly, combination therapy protocols are achieving objective responses in both hematological malignancies and solid tumors. Table 3 contains a list of drug combinations and indications in active HDACi combination therapy trials.

Monotherapy trials

Modesitt *et al.* [68] in a Gynecologic Oncology Group study of vorinostat in patients with recurrent or persistent epithelial ovarian or primary peritoneal carcinoma who were platinum-resistant/refractory concluded that vorinostat was well tolerated but had minimal activity in this patient population. Richardson *et al.* [61] in a phase I trial of vorinostat in patients with relapsed/refractory multiple myeloma concluded that vorinostat was generally well tolerated and had modest single-agent activity, warranting investigation with other antimyeloma agents. Garcia-Manero et *al.* [62] studied vorinostat in patients with advanced leukemias and myelodysplastic syndromes (MDS) and observed seven of 41 patients, all with AML, had hematological improvement including two complete responses and two complete responses with incomplete blood count recovery. They observed that antioxidant gene expression may confer vorinostat resistance, and that further evaluation of vorinostat in AML/ MDS is warranted. Steele *et al.* [60] observed stable disease in 18 of 46 patients in a phase I trial of belinostat in patients with advanced solid tumors. Schrump *et al.* [109] studied romidepsin in a lung cancer phase II trial that included assessment of gene expression profiles pre-romidepsin and post-romidepsin treatment in laser-captured tumor cells and adjacent normal bronchial epithelial cells. Although no objective responses were

observed, transient disease stabilization was noted in nine of 18 evaluable patients, and there was evidence of gene expression changes indicating a shift of the lung tumor cells toward the expression pattern of normal bronchial epithelia. In a phase I trial of MGCD0103 in solid tumors disease stabilization was observed in five of 32 evaluable patients [59], and in a MGCD0103 phase I in leukemia three of 39 patients achieved a complete bone marrow response including two patients who had been previously treated with chemotherapy for refractory AML [58].

Combination therapy trials

Sung and Waxman [120] reported a phase I trial of escalating doses of 5-fluorouracil in combination with a fixed dose of phenylbutyrate in patients with advanced colorectal cancer. They reported disease stabilization in three out of four patients who completed at least 8 weeks of treatment. Soriano *et al.* [118•] conducted a phase I/II study of VPA, 5-azacytidine, and all-*trans* retinoic acid (ATRA) in patients with AML or high-risk MDS. The overall response rate was 42%, and the response rate in previously untreated patients older than 60 years was 52%. Clinical activity was associated with global DNA hypomethylation and histone acetylation, but these epigenetic changes were not different between responders and nonresponders. Higher VPA levels were demonstrated in patients who responded versus patients who did not, suggesting the potential utility of targeting plasma levels of VPA rather than dosing based on weight.

Munster *et al.* [113•] have studied the potentiation of tumor cell sensitivity to topo II inhibitors by HDACi, which they have demonstrated is associated with HDACi-induced chromatin remodeling increasing access of topo II inhibitor to the DNA substrate. They have examined this combination in a phase I dose-escalation trial of VPA and epirubicin in advanced solid tumor patients. Partial responses were seen in 22% of patients and stable disease/minor responses were seen in 39% of patients. The authors concluded that noteworthy antitumor activity was observed in heavily pretreated patients and historically anthracycline-resistant tumors. Decitabine alone or in combination with VPA was studied by Blum *et al.* in AML [114]. The authors determined the optimal biological dose of decitabine based on gene reexpression and the maximum tolerated dose of VPA combined with decitabine. Of evaluable patients 52% responded. Reexpression of estrogen receptor was associated with clinical response. Low-dose decitabine showed promising activity. However, the addition of VPA at relatively low doses resulted in encephalopathy. The authors concluded that further studies of decitabine alone or with an alternate HDACi are warranted. Ramalingam *et al.* [78] studied vorinostat in combination with carboplatin and paclitaxel for advanced solid malignancies. Of 25 evaluable patients they observed partial responses in 11, including 10 of 19 NSCLC patients and one patient with head and neck cancer, all chemotherapy naive. They are currently conducting a randomized phase II of carboplatin and paclitaxel with either vorinostat or placebo in advanced NSCLC.

Conclusion

HDACi with broad isoform inhibitory activity or some degree of isoform selectivity are moving into clinical trial in a wide range of indications and combinations. Despite only

modest evidence of single-agent activity, especially in solid tumors, the pace of clinical exploration of HDACi is markedly accelerating. There is reason to be encouraged by recent advances in understanding of HDACi mechanisms of action, selection of optimal indications, and identification of rational combinations and optimal trial design.

The clinical development of HDACi presents an instructive dichotomy. Histone acetyltransferases, HDACs, and the regulation of acetylation have been the subject of highly sophisticated molecular analyses, often at the level of a single gene locus, so that on a reductionist basis, this class of drug is exceptionally well understood. In contrast, to employ HDACi clinically, it is important to recognize that these drugs are highly pleiotropic and their impact should, therefore, be examined for impact on a systems level, including recognition of their activity as modulators of cell metabolism, the immune system and the vasculature. Recent events suggest we are entering a new, more mature phase of HDACi clinical development that will facilitate a comprehensive examination of this molecularly fascinating but imperfectly understood class of drug.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have

been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 724–726).

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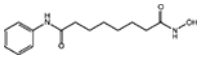
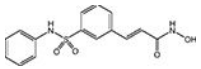
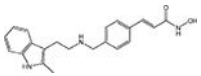
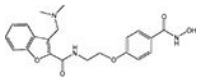
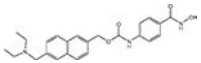
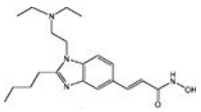
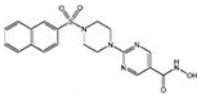
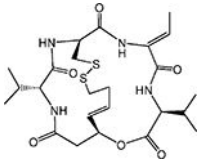
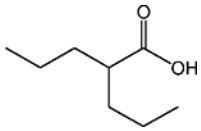
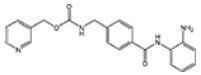
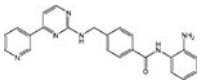
Table 1

Histone deacetylase inhibitors in clinical trial

Class	Compound	Structure	Isotype selectivity[a,b]	Company	Stage
Hydroxamic acid	Vorinostat/Zolinza (SAHA)		Class I, IIa, IIb, IV	Merck	USFDA approval for CTCL
	Belinostat/PXD101		Class I, IIa, IIb, IV	TopoTarget	Phase II
	Panobinostat/LBH589		Class I, IIa, IIb, IV	Novartis	Phase III
	CRA-024781 (PCI 24781)		Class I, IIb	Celera Genomics	Phase I
	ITF2357		Class I, II Class I, II	Italfarmaco	Phase II
	SB939		ND	S*BIO	Phase I
	R306465 (JNJ-16241199)		Class I	Johnson & Johnson	Phase I
Cyclic peptide	Romidepsin/depsi peptide (FK 228)		HDAC 1, 2, 4, 6	Gloucester	Phase II

Class	Compound	Structure	Isotype selectivity[a,b]	Company	Stage
Aliphatic acid	VPA		Class I, IIa	G2M	Phase II
Benzamide	SNDX-275/entinostat (MS-275)		HDAC 1, 2, 3, 9	Syndax/Bayer Schering Pharma AG	Phase II
	MGCD0103		HDAC 1, 2, 3, 11	MethylGene	Phase II

CTCL, cutaneous T-cell lymphoma; HDAC, histone deacetylase; ND, isotype selectivity not known; USFDA, US Food and Drug Administration; VPA, valproic acid.

[a]Class I: HDAC 1, 2, 3, 8; class IIa: HDAC 4, 5, 7, 9; class IIb: HDAC 6, 10; class IV: HDAC 11.

[b]Data in this table are derived from references [9,11,14–17].

Table 2

Published histone deacetylase inhibitors clinical trials January 2007–June 2008[a]

HDACi	Combination drug(s)	Phase	Indication	References
Vorinostat	None	I	Advanced multiple myeloma	[61]
	None	I	Advanced leukemias and MDS	[62]
	None	I	GI cancer (Japanese patients)	[63]
	None	I	Children with refractory solid tumors	[64]
	None	I	Solid tumors (Japanese patients)	[65]
	None	I	NHL (Japanese patients)	[66]
	None	I	Malignant gliomas	[67]
	None	II	Refractory CTCL	[13••]
	None	II	Persistent or recurrent epithelial ovarian or primary peritoneal carcinoma	[68]
	None	II	Relapsed or refractory breast, colorectal, or NSCLC	[69]
	None	II	Recurrent and/or metastatic head and neck cancer	[70]
	None	II	Recurrent/metastatic TCC failing first line platinum-based therapy	[71]
	None	II	Relapsed NSCLC	[72]
	None	II	Recurrent GBM	[73]
	None	II	HRPC	[74]
	None	II	Relapsed or refractory indolent NHL	[75]
	None	II	Relapsed DLBCL	[76]
	None	II	Metastatic breast cancer	[77]
	None	IIb	Persistent, progressive, or treatment refractory CTCL	[12••]
	Carboplatin and paclitaxel	I	Advanced solid malignancies	[78]
	13cRA	I	Children with refractory neuroblastomas, medulloblastomas, PNETs, and atypical teratoid rhabdoid tumor	[79]
	Bortezomib	I	Relapsed/refractory multiple myeloma	[80]
	Bortezomib	I	Refractory solid tumors	[81]
	Bevacizumab	I	Kidney cancer	[82]
	Capecitabine	I	Advanced solid tumors	[83]
	Bexarotene	I	Advanced CTCL	[84]
	Gemcitabine and cisplatin/carboplatin	I	Advanced NSCLC	[85]
	Doxorubicin	I	Advanced solid tumors	[86]

HDACi	Combination drug(s)	Phase	Indication	References
	Idarubicin	I	Advanced acute leukemia	[87]
	Pemetrexed and cisplatin	I	Advanced cancer	[88]
	Azacitidine	I/II	MDS, AML	[89]
	Tamoxifen	II	Advanced breast cancer having failed prior aromatase inhibitor therapy	[90]
PCI-24781	None	I	Refractory advanced solid tumors	[91]
R306465	None	I	Advanced tumors	[92]
LBH-589	None	I	Advanced solid tumors or NHL	[93]
	None	I	Advanced solid tumors or lymphoma	[94]
	W/wo docetaxel and prednisone	I	Castration-resistant prostate cancer	[95]
SNDX-275	None	I	Refractory and relapsed acute leukemias	[56]
	None	I	Refractory solid tumors and lymphoid malignancies	[57]
	Azacitidine	I	Advanced NSCLC	[96]
MGCD0103	None	I	Advanced leukemia, MDS	[97]
	None	I	Advanced solid tumors	[59]
	None	II	Relapsed or refractory NHL	[98]
	None	II	Relapsed or refractory NHL	[99]
	Gemcitabine	I/II	Refractory solid tumors	[100]
	Azacitidine	I/II	High-risk MDS or AML	[101]
Belinostat	None	I	Advanced solid tumors	[60]
	None	I/II	Unresectable hepatocellular carcinoma	[102]
	None	II	Metastatic or recurrent platinum-resistant (<6 months) EOC and LMP ovarian tumors	[103]
	Azacitidine	I	Advanced myeloid neoplasms	[104]
	Carboplatin and paclitaxel (BelCaP)	II	Relapsed EOC	[105]
Romidepsin	None	I	Thyroid and other advanced cancers	[106]
	None	II	CTCL, PTCL	[107]
	None	II	Metastatic HRPC	[108]
	None	II	Lung cancer	[109]
	Gemcitabine	I	Pancreatic and other advanced solid tumors	[110]
ITF2357	None	II	Relapsed/refractory Hodgkin’s lymphoma	[111]
VPA	None	I	Refractory advanced cancer	[112]
	Epirubicin	I	Advanced solid tumors	[113•]

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HDACi	Combination drug(s)	Phase	Indication	References
	Decitabine	I	AML	[114]
	Decitabine	I	NSCLC	[115]
	Azacytidine	I	Advanced solid cancers	[116]
	FEC100	I/II	Locally advanced/metastatic breast cancer.	[117]
	Azacitidine, ATRA	I/II	AML, MDS	[118•]
	Hydralazine	II	Refractory solid tumors	[119]

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EOC, epithelial ovarian cancer; GBM, glioblastoma multiforme; GI, gastrointestinal; HDACi, histone deacetylase inhibitors; HRPC, hormone refractory prostate cancer; LMP, low malignant potential; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; NSCLC, nonsmall cell lung cancer; PNETs, primitive neuroectodermal tumors; PTCL, peripheral T-cell lymphoma; TCC, transitional cell urothelial cancer; VPA, valproic acid.

[a]Summary of active HDACi clinical trials. References are to full-length papers or to abstracts from the 2007 and 2008 annual meetings of the American Society of Clinical Oncology.

Table 3

Active histone deacetylase inhibitors clinical trials[a]

HDACi	Combination drug(s)	Indication
Vorinostat	Azacitidine, bortezomib, decitabine, docetaxel, 5-FU, doxorubicine, idarubicin, erlotinib, isotretinoin, gemcitabine, temozolomide, sorafenib, tamoxifen, flavopiridol, paclitaxel/bevacizumab, paclitaxel/carboplatin, gemcitabine/cisplatin or carboplatin, 5-FU/leucovorin calcium/ oxaliplatin, isotretinoin/carboplatin, cytarabine/etoposide, irinotecan/5-FU/leucovorin, rituximab/ifosfamide/carboplatin/etoposide, radical prostatectomy, palliative radiotherapy	CTCL, GBM, RCC, MDS, AML, ALL, CML, breast cancer, NSCLC, melanoma, lymphoma, advanced malignant pleural mesothelioma, advanced solid tumors, gliomas, nasopharyngeal cancer or nasal natural killer T-cell lymphoma, multiple myeloma, NHL, leukemia, colorectal cancer, GI cancer, prostate cancer, pelvic malignancy
Romidepsin	Decitabine, flavopiridol, gemcitabine, bortezomib	CTCL, PTCL, squamous cell carcinoma of the head and neck, NHL, refractory thyroid cancer, pulmonary and pleural malignancies, pancreatic, advanced solid tumors, relapsed myeloma, advanced lung, esophageal or pleural cancer
Belinostat	Azacitidine, bortezomib, isotretinoin, carboplatin/paclitaxel	Hepatocellular carcinoma, primary peritoneal cancer, fallopian tube cancer, B-cell NHL, T-cell lymphomas, MDS, thymic carcinoma, advanced hematological cancers, advanced solid tumors, lymphomas, ovarian cancer
LBH589	Ketoconazole, bortezomib, trastuzumab, dextromethorphan, gemcitabine, lenalidomide/dexamethasone, capecitabine/lapatinib, paclitaxel/carboplatin/bevacizumab	CTCL, CML, MDS, NSCLC, advanced hematological malignancies, clear cell renal carcinoma, advanced solid tumors, multiple myeloma, breast cancer, malignant pleural mesothelioma
SB939	None	Advanced or metastatic solid tumors
ITF2357	None	Relapsed/refractory Hodgkin's lymphoma
PCI-24781 (CRA-024781)	None	Advanced cancer
SNDX-275	Azacitidine, erlotinib, sargramostim (GM-CSF), exemestane	NSCLC, AML, CML, MDS, breast cancer
MGCD0103	Azacitidine, docetaxel, gemicitabine	AML, MDS, CLL, lymphoma, solid tumors, Hodgkin's lymphoma, NHL
VPA	Decitabine, bevacizumab, doxorubicin, etoposide, epirubicin, sunitinib, sorafenib, dasatinib, erlotinib, lapatinib, lenalidomide, karenitecin, azacitidine/carboplatin, azacitidine/ATRA, ATRA/theophyllamine, FEC 100 (5-FU, epirubicin, and cyclophosphamide), temozolomide/radiation therapy	CLL, AML, MDS, GBM, small lymphocytic lymphoma, advanced thyroid cancer, nasopharyngeal carcinoma, ovarian cancer, NHL, advanced solid tumors, melanoma, advanced breast cancer, malignant mesothelioma, neuronal tumors and brain metastases

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CML, chronic myelogenous leukemia; CTCL, cutaneous T-cell lymphoma; EOC, epithelial ovarian cancer; 5-FU, 5-fluorouracil; GBM, glioblastoma multiforme; GI, gastrointestinal; HDACi, histone deacetylase inhibitors; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; NSCLC, nonsmall cell lung cancer; PTCL, peripheral T-cell lymphoma; RCC, renal cell carcinoma; VPA, valproic acid.

[a]Further information regarding these clinical trials can be found at (http://www.cancer.gov/search/SearchClinicalTrialsAdvanced.aspx).