# The Use of Histone Deacetylase Inhibitors for the Treatment of Solid Tumors

*a report by*

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'Epigenetics' is a term used to describe heritable states of gene expression that are not due to changes in DNA sequence. Epigenetic phenomena have been shown to play an important role in carcinogenesis and tumor progression. Such phenomena also represent potential therapeutic targets for cancer treatment as they are potentially reversible. Two such phenomena are epigenetic changes in DNA methylation, resulting in altered genetic expression, and histone modifications.[1] This article focuses on histone modifications and the balance of acetylation/deacetylation in tumor cells as a therapeutic target for anticancer therapies.

## Background

DNA wraps around a core of eight histone proteins (pairs of H2A, H2B, H3, and H4) to form nucleosomes. Lysine residues on histones are a target of acetylation, via histone acetyltransferases (HATs), and deacetylation, via histone deacetylases (HDACs). Acetylation neutralizes the positive charge of the lysine ε-amino group of the core histone tail. Put simply, this results in an 'unwrapped' DNA conformation, allowing access to DNA by transcription factors and co-activators. Deacetylation of lysine residues leads to tighter packaging of DNA and silencing of transcription.[1]

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Mutations in HATs and recruitment of HDACs have both been associated with transcriptional repression of genes, resulting in cell growth and neoplastic transformation.[2] These enzymes also have non-histone substrates, including transcription factors and other proteins, and the balance of acetylation/deacetylation can influence protein stability, protein localization, binding of transcription factors to DNA, and apoptosis.

There are four classes of HDAC, with class I, II, and IV HDACs possessing a catalytic domain with a zinc pocket, which is important for the binding of HDAC inhibitors (HDACi). Zinc-independent and nicotinamide adenine dinucleotide (NAD)-dependent class III HDACs are not affected by the HDACi currently in clinical development. Class I HDACs are found mainly in the nucleus, while class II HDACs (4, 5, 6, 7, 9, and 10) are seen in both the nucleus and the cytoplasm.[3,4] The class IV family consists of HDAC11, which shares features of both class I and class II enzymes.[4]

Several classes of HDACi have been identified (see *Table 1*):[5,6]

- short-chain fatty acids, such as phenylbutyrates;[7]
- hydroxamic acids, including trichostatin A (TSA);[8]
- vorinostat (suberoylanilide hydroxamic acid (SAHA)),[9] oxamflatin, belinostat (PXD101), LAQ824, and LBH589;
- cyclic tetrapeptides containing a 2-amino-8-oxo-9, 10-epoxy-decanoyl (AOE) moiety, trapoxin A;[10]
- cyclic peptides not containing the AOE moiety, romidepsin (depsipeptide, FK228), and apicidin;[11] and
- benzamides, including MS-275 (SNDX-275) and MGCD0103.[12]

This article focuses on HDACi in the treatment of solid tumors. Since the only US Food and Drug Administration (FDA)-approved HDACi to date is vorinostat, which was approved for use in cutaneous T-cell lymphoma (CTCL), the data leading to its approval are also presented here. Otherwise, the focus is on research in solid tumors; information on trials examining HDACi in hematological malignancies, including lymphoma, is not included. This article is not designed to discuss each HDACi in detail, but to present an overview of the available clinical data on HDACi, focusing on phase II trials.

## Phase II Data for Single-agent Histone Deacetylase Inhibitors

### *Vorinostat*

To date, vorinostat is the only HDACi approved by the FDA for the treatment of malignancy. It is an orally active and potent inhibitor of HDAC activity, inhibiting both class I (HDAC1, HDAC2, HDAC3) and class II (HDAC 6)

HDACs at nanomolar concentrations. It was approved in October 2006 for the treatment of cutaneous manifestations of CTCL in patients with progressive, persistent, or recurrent disease, or following two systemic therapies (www.fda.gov/cder/Offices/OODP/whatsnew/vorinostat.htm). This approval was based on the results of two open-label clinical trials.

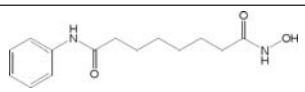
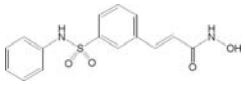
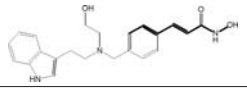
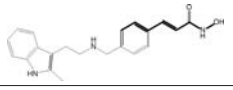
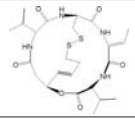
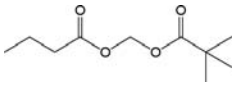
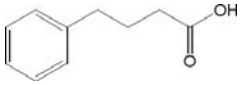
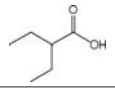
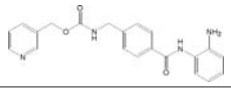
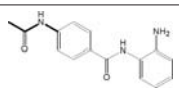
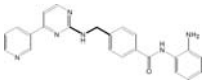
The pivotal study supporting FDA approval was an open-label trial that enrolled 74 patients with stage IB–IVA CTCL who had received at least two prior systemic therapies. Patients were treated with 400mg oral vorinostat daily until disease progression or intolerable toxicity resulted. The primary end-point of the study was objective response rate (ORR), with secondary end-points of time to response (TTR), time to progression (TTP), duration of response (DOR), and relief of pruritis. ORR was 29.7%, with median DOR not reached but estimated to be ≥185 days; median TTP was 4.9 months, and 32% of patients reported relief of pruritis. The most common drug-related adverse events were diarrhea, fatigue, nausea, and anorexia, but ≥grade 3 events included fatigue (5%), pulmonary embolism (5%), thrombocytopenia (5%), and nausea (4%).[13]

The other phase II study providing supporting evidence for approval of vorinostat enrolled 33 patients with CTCL refractory to or intolerant of conventional therapy. Patients had received a median of five prior therapies. Thirteen of these patients were treated with oral vorinostat 400mg daily (Group 1). The other participants received different dosing regimens of vorinostat. For the 13 patients in Group 1, the overall response rate was 31%. In Group 1, the most common drug-related adverse events were fatigue, thrombocytopenia, nausea, and diarrhea, with ≥grade 3 or 4 adverse events including thrombocytopenia in one patient, anemia in one patient, and dehydration in one patient, as well as some ≥grade 3 chemistry abnormalities.[14] The FDA reviewers believed that the observed 30% ORR of skin disease with a median DOR of 168 days (or more) in a population of heavily pre-treated advanced CTCL patients was consistent with clinical benefit.

Phase II trials of oral vorinostat have been conducted in patient populations with solid tumors as well. In a California Cancer Consortium (CCC) study, vorinostat was administered to 14 patients with metastatic breast cancer at a dose of 200mg twice daily for 14 of 21 days per cycle. No responses were observed, but four patients (29%) had stable disease (SD) for a median of ≥8.7 months (four to 13 months). Toxicities included fatigue, diarrhea, nausea, mucositis, and lymphopenia.[15] A similar treatment dose and schedule were used in a study of 68 patients with recurrent glioblastoma multiforme (GBM). The primary efficacy end-point of this study was a six-month progression-free survival rate (PFS6 rate) of 25%. At the time of the planned interim analysis, which included the first 22 patients, five patients were progression-free at six months for a PFS6 rate of 23%, which, according to the authors, met the trial's prospectively defined primary efficacy end-point. The most common adverse events included fatigue, diarrhea, dehydration, and thrombocytopenia.[16]

Two other trials examined the 400mg daily dose of oral vorinostat. Early results have been reported for a study sponsored by the Prostate Cancer Clinical Trials Consortium (PCCTC). Twenty-three patients had been enrolled, but only nine were evaluated for response at the time of the report. Of these nine patients, three had SD.[17] In a phase II study of vorinostat in non-small-cell lung cancer (NSCLC) patients with relapsed disease who had progressed through ≤1 prior cytotoxic therapy, data have been presented on the first 14 patients treated. In 12 patients evaluable for response, no ORs occurred, but seven patients (58%) had SD. Median overall survival (OS) was 6.5 months, with an estimated six-month OS rate of 50% (standard error (SE) 16%). In addition to the expected toxicities, four of 14 patients evaluable for safety experienced adverse vascular events, including two patients with pulmonary embolism and one patient with a fatal cardiovascular accident (CVA).[18]

**Table 1: Histone Deacetylase Inhibitors in Clinical Trials**

| Class | Compound | Structure | Phase |
|---|---|---|---|
| Hydroxamic acid | SAHA |  | Approved |
| | PXD101 |  | II |
| | LAQ824 |  | I |
| | LBH589 |  | II |
| Cyclic peptide | FK-228 |  | II |
| Aliphatic acid | AN-9 |  | II |
| | PB |  | II |
| | VP |  | II |
| Benzamide | MS-275 |  | II |
| | CI-994 |  | III |
| | MGCD 0103 |  | II |

In addition to a phase III compassionate-use trial of vorinostat for patients with advanced CTCL, there is an ongoing phase III trial of vorinostat in patients with mesothelioma in whom treatment with pemetrexed has failed.[19] Currently, phase II or phase I/II trials are investigating vorinostat as a single agent in melanoma, stage IIIb or IV NSCLC, renal cell carcinoma, and transitional cell carcinoma of the urothelium, and as neoadjuvant therapy in women with stage I–III breast cancer (www.cancer.gov/clinicaltrials).

### *Romidepsin*

Romidepsin (depsipeptide, FK228), a cyclic peptide HDACi, is also being evaluated in clinical trials for the treatment of CTCL, but we focus here on clinical trials in solid tumors.

**Table 2: Clinical Combination of Histone Deacetylase Inhibitors and Other Drugs Reported in the Literature**

| HDACi | Combination Drug(s) | Tumor Type | Phase | Citation |
|---|---|---|---|---|
| Vorinostat | Carboplatin, paclitaxel | Solid tumors | I | a |
| | 5-FU, leucovorin, oxaliplatin (FOLFOX) | Colorectal cancers | I | b |
| | Temozolomide | Malignant gliomas | I | b |
| | Doxorubicin | Advanced solid tumors | I | b |
| | Bortezomib | Refractory solid tumors | I | b |
| | Capecitabine | Advanced solid tumors | I | b |
| | Pemetrexed, cisplatin | Advanced cancers | I | b |
| VPA | 5-AZA | Solid tumors | I | b |
| | Epirubicin | Advanced solid tumors | I | 28 |
| | 5-FU,epirubicin, cyclophosphamide (FEC100) | Advanced metastastic breast cancer | I/II | b |
| MS-275 | ATRA | Solid tumors | I | a |
| CI-994 | Gemcitabine | Solid tumors | I | 29 |
| | Gemcitabine | Pancreatic | II | 30 |
| | Gemcitabine | Non-small-cell lung cancer | II | c |
| | Capecitabine | Solid tumors | I | 31 |
| | Carboplatin, paclitaxel | Solid tumors | I | 32 |
| | Carboplatin, paclitaxel | Non-small-cell lung cancer | II | d |
| Belinostat | 5-FU | Advanced solid tumors | Ib/II | b |
| | Carboplatin, paclitaxel | Advanced solid tumors | Ib/II | b |

*HDACi = histone deacetylase inhibitors; a = 2006 American Society of Clinical Oncology (ASCO) Annual Meeting abstract; b = 2007 ASCO Annual Meeting abstract; c = 2002 ASCO Annual Meeting abstract; d= 2003 ASCO Annual Meeting abstract.*

Phase II data on romidepsin have been reported for patients with chemotherapy-naïve metastatic hormone-refractory prostate cancer (HRPC) and patients with squamous cell carcinoma of the head and neck (SCCHN).[20,21] Both studies used a regimen of romidepsin 13mg/m$^2$ given as an intravenous (IV) infusion on days one, eight, and 15 of a 28-day cycle. Final results are available for the HRPC study. The primary end-point was the rate of disease control achieved (complete response (CR) + partial response (PR) + SD for six months). Thirty-one patients were enrolled, but only 21 were evaluable for both radiological and prostate-specific antigen (PSA) responses. One patient had a PR lasting >6 months and two had SD for six months, giving a disease control rate of 14%: the PSA response rate was only 7%. The most common adverse events associated with romidepsin in this study were nausea, vomiting, fatigue, anorexia, constipation, diarrhea, dysguesia, and myelosuppression.

Due to reports of lethal cardiac necrosis in pre-clinical studies, specific monitoring for cardiac toxicity has been included in clinical trials of romidepsin. In this phase II study, non-specific asymptomatic ST-segment changes on electrocardiograph (ECG) were seen in 15% of patients, but there was no evidence of significant QTc prolongation confirmed by manual calculation, and only minimal cardiac toxicity was reported.[20] Efficacy data from the trial of romidepsin in SCCHN are not available. So far, fatigue and weakness are the most common toxicities, with myelo-suppression being uncommon. No significant cardiovascular toxicities attributed to romidepsin have been reported, except for grade 3 hypotension in one patient.[21]

Romidepsin is also undergoing phase II or phase I/II investigation as a single agent in patients with recurrent high-grade gliomas and in patients with progressive recurrent and/or metastatic non-medullary thyroid carcinoma refractory to radioactive iodine (www.cancer.gov/clinicaltrials).

A phase II study of romidepsin in patients with metastatic neuroendocrine tumors was terminated prematurely due to the occurrence of several serious cardiac adverse events in the 15 patients treated. These included a sudden death attributed to possible ventricular arrhythmia, asymptomatic grade 2 ventricular tachycardia in two patients, and prolonged QTc in three patients.[22] As noted above, such significant cardiac toxicity has not been noted in other clinical trials of romidepsin in treatment of solid tumors.

### *Other Histone Deacetylase Inhibitors*

CI-994 is an oral benzamide HDACi that had low response rates when used as a single agent in two phase II studies conducted in the 1990s.[23,24] One enrolled 32 patients with stage IIIb or IV NSCLC and <1 prior chemotherapy regimen, including adjuvant chemotherapy; CI-994 was given as an 8mg/m$^2$ daily dose. Of 29 patients evaluable for response, there were only two PRs (7% ORR), although eight patients (28%) had SD for >8 weeks. Median TTP was eight weeks with a median survival of 30 weeks. Common adverse events included fatigue, anorexia, nausea, vomiting, paresthesia, and thrombocytopenia.[23] Another trial used the same dosage and schedule of CI-994 in patients with chemotherapy-naïve metastatic renal cell carcinoma (RCC). Forty-eight patients were enrolled, with 45 evaluable for response; no PR or CR was observed, but 26 patients (58%) had SD for >8 weeks with a median duration of SD 23 weeks. Median TTP was 15 weeks and median survival 48 weeks. Adverse events were similar to those reported in the NSCLC trial.[24]

MS-275 is another oral benzamide HDACi and has been assessed as a single agent as a treatment for metastatic melanoma. Twenty-eight patients were randomized to receive either MS-275 3mg bi-weekly (days one and 15 of a 28-day cycle) or MS-275 7mg weekly for three weeks out of four (days one, eight, and 15 of a 28-day cycle). No objective tumor responses were observed, but 29% in the 3mg dose group and 21% in the 7mg dose group had SD lasting from eight to 48 weeks. The most frequently reported adverse events were nausea, diarrhea, and hypophosphatemia.[25]

Pivaloyloxymethyl butyrate (Pivanex, AN-9) is a prodrug of the short-chain fatty acid butyrate. In a multicenter phase II trial, AN-9 was administered at 2.34g/m$^2$ as a six-hour IV infusion daily for three days every 21 days to 47 patients with refractory NSCLC. Three patients (6.4%) had a PR, while 14 (30%) had SD lasting 12 weeks: median OS was 6.2 months, with one-year OS 26%. The most common toxicities were fatigue, nausea, and dysgeusia.[26]

A few other active phase II trials assessing HDACi as single-agent therapy are examining belinostat (PXD101) in unresectable hepatocellular carcinoma,[27] oral LBH589 in refractory CTCL, and valproic acid in advanced thyroid cancer.

## Rationale for Combination Therapy

While in many trials response rates in solid tumors have not been impressive, a significant amount of stable disease has been noted, leading to interest in the assessment of HDACi in combination with other

agents. Many clinical trials evaluating HDACi as part of combination therapy in a variety of solid tumors have been reported or are now under way (see *Tables 2* and *3*). Given that HDACi may lead to re-expression of genes restoring normal function to tumor cells and can result in growth arrest, differentiation, and/or apoptosis in tumor cells, these agents could potentially increase the efficacy of other therapies, such as radiation and cytotoxic chemotherapy.

There is pre-clinical evidence to support this. For example, vorinostat enhanced radiation-induced apoptosis and reduced tumor survival after radiation exposure in human prostate and glioma cell lines.[33] Several HDACi were shown to enhance sensitivity to ionizing radiation in two human squamous carcinoma cell lines previously characterized as intrinsically resistant to radiation, with some evidence to suggest a mechanism of action involving cell cycle arrest in the G1 phase and inhibition of DNA synthesis.[34] In a xenograft model using a human prostate tumor cell line, the combination of MS-275 with radiation resulted in greater than additive inhibition of tumor growth compared with MS-275 or radiation alone.[35]

HDACi have been investigated in human tumor cell lines in combination with various cytotoxic chemotherapy agents. Sodium butyrate significantly increased induction of apoptosis when combined with either vincristine or cisplatin in two human retinoblastoma cell lines,[36] as well as resulting in hypersensitivity to etoposide in two human leukemia cell lines.[37] In two human breast cancer cell lines, LAQ824 not only enhanced apoptosis induced by docetaxel and epothilone B, but also significantly increased apoptosis induced by the monoclonal antibody trastuzumab.[38] The HDACi AN9 combined with doxorubicin synergistically inhibited the growth of NSCLC and B-cell lymphoma cells.[39]

DNA methyltransferase inhibitors also affect an epigenetic pathway, so there is significant interest in combining these agents with HDACi, especially in light of the results of some pre-clinical studies. For example, in one study decitabine, a methyltransferase inhibitor, was shown to greatly enhance apoptosis induced by romidepsin or TSA in several human lung cancer cell lines.[40] Such combinations are already being examined in clinical trials for solid tumors (see *Table 3*) and hematological malignancies, and data have been reported on a clinical trial using decitabine in combination with the HDACi sodium phenylbutyrate (PB) in patients with acute myeloid leukemia and those with myelodysplastic syndrome.[41]

## Discussion

HDACs are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. Hypoacetylation of histones has been observed in a number of tumor types, and HDACi have shown promising activity in *in vitro* and *in vivo* models. Treatment of tumor cell lines and xenografts with HDACi results in growth arrest, changes in cell cycle distribution, and apoptosis. For example, treatment of human leukemia cell lines with MS-275 resulted in potent antiproliferative activity, with the induction of p21CIP1/WAF1-mediated growth arrest and expression of differentiation markers (CD11b) at lower concentrations.[42] At higher concentrations of MS-275 there is a marked induction of reactive oxygen species, mitochondrial damage, caspase activation, and apoptosis.[42] Treatment of sensitive tumor cell lines with MS-275 induces gelsolin, a maturation marker, and produces a change in the cell cycle distribution with a decrease in S-phase and an accumulation of cells in G1.[12]

HDACi represent an interesting class of anticancer agents that target the reversible epigenetic phenomenon of hypoacetylation of histones, thus reversing repression of gene transcription. Even though this is the postulated mechanism, the precise mechanism of action of HDACi is currently unknown. A number of clinical trials have assessed target

**Table 3: Histone Deacetylase Inhibitors in Combination Therapy in Solid Tumors**

| HDACi | Combination Drug(s) | Tumor Type | Phase |
|---|---|---|---|
| Vorinostat | Tamoxifen | Breast cancer | II |
| | Herceptin | Breast cancer | I/II |
| | Paclitaxel, bevacizumab | Breast cancer | I/II |
| | Bevacizumab | Renal cell carcinoma | I/II |
| | Isotretinoin | Renal cell carcinoma, solid tumors | I/II |
| | 5-FU, leucovorin | Colorectal cancer | I/II |
| | 5-FU, leucovorin calcium, oxaliplatin | Colorectal cancer | I/II |
| | Carboplatin, paclitaxel | Non-small-cell lung cancer | II |
| | Erlotinib | Non-small-cell lung cancer | I/II |
| | Capecitabine | Solid tumors | I |
| | Bortezomib | Solid tumors | I |
| | Gemcitabine | Solid tumors | I |
| | Temozolomide | Malignant gliomas | I |
| | Flavopiridol | Advanced solid tumors | I |
| | Decitabine | Advanced solid tumors | I |
| | Doxorubicin | Advanced solid tumors | I |
| | Azacitidine | Nasopharyngeal carcinoma | I |
| | Irinotecan, fluorouracil, leucovorin (FOLFIRI) | Advanced upper gastrointestinal cancers | I |
| Romidepsin | Gemcitabine | Pancreatic and solid tumors | I/II |
| | Decitabine | Pulmonary and pleural malignancies | I |
| | Flavopiridol | Lung, esophageal cancer, mesothelioma, or lung or pleural metastases | I |
| MS-275 | Azacitidine | Non-small-cell lung cancer | I/II |
| Valproic acid | Karenitecin | Melanoma | I/II |
| | Azacitidine, carboplatin | Ovarian cancer | I/II |
| | 5-FU, epirubicin, cylclophosphamide | Breast cancer | II |
| | Temozolomide, radiotherapy | Glioblastoma multiforme | II |
| | Etoposide | Neuronal tumors and brain metastases | I |
| | Bevacizumab | Advanced solid tumors | I |
| Belinostat | Carboplatin, paclitaxel | Ovarian cancer | I/II |
| | Bortezomib | Solid tumors | I |
| | Isotretinoin | Solid tumors | I |
| | 17-AAG | Solid tumors | I |
| | 5-FU | Solid tumors | I |
| MGCD0103 | Gemicitabine | Solid tumors, pancreatic cancer | I/II |
| | Docetaxel | Advanced solid tumors | I |
| LBH589 | Docetaxel, prednisone | Hormone refractory prostate cancer | I |
| | Gemcitabine | Solid tumors | I |

*Source: http://www.cancer.gov/search/SearchClinicalTrialsAdvanced.aspx*

modulation and the pharmacodynamic effect of HDACi therapy by using the level of acetylation of lysine residues in peripheral blood mononuclear cells (PBMCs) pre- and post-treatment. Recently, a multiparameter flow cytometry assay has been developed to assess the contribution of individual cell types (T cells, B cells, monocytes) in the observed response to HDACi therapy in PBMCs.[43] However, up to this point pharmaco-dynamic assays in PBMCs have not been shown to correlate with clinical efficacy in solid tumor trials.

As mentioned above, there are multiple ongoing trials of HDACi in solid tumors, both as single agents and in combination with other agents. Given the postulated mechanism of action and the fact that carcinogenesis is a multistep process with complex derangements in normal function, the likely role of this class of agents will be in combination for the treatment of solid tumors. HDACi therapy is already showing considerable promise in clinical trials in leukemia in combination with agents such as 5-azacytidine. There is hope that using HDACi in combination with other therapies will result in benefits for patients with solid tumors as well. ■

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### Conflicts of Interest

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