The development of cancer is a multistep process that involves multiple genetic and epigenetic alterations within the tumor and microenvironment. Histone acetylation and deacetylation of the core nucleosomal histones is an important mechanism regulating gene transcription. Defects in the enzymes regulating histone acetylation, namely, the histone acetyltransferases (HAT) and histone deacetylases (HDAC), have been described for both hematologic and solid tumor malignancies (1). Inhibitors of HDAC activity induce cell differentiation, growth arrest and/or apoptosis, and autophagy, as well as antiangiogenic effects (1). Richon and colleagues (2) showed that the novel hydroxamate HDAC inhibitor (HDACi), vorinostat [Zolinza; Merck; originally called suberoylanilide hydroxamic acid (SAHA)], induced differentiation, growth arrest, or apoptosis of transformed human cells in culture at micromolar concentrations. Vorinostat was originally identified based on its ability to induce differentiation of murine erythroleukemia cells (2). Subsequently, it was found to induce differentiation of human breast adenocarcinoma cells and growth arrest in human prostate carcinoma and bladder transitional cell carcinoma cells and block prostate cancer growth in in vivo studies (3). This work prompted the development of vorinostat as a therapeutic agent. The initial phase I intravenous formulation of vorinostat was shown to be well tolerated at doses that caused the accumulation of acetylated histones in peripheral blood mononuclear cells and antitumor effects (4). Following the intravenous formulation, an oral formulation was subsequently developed to provide improved patient convenience. The initial phase I study of oral vorinostat evaluated once- or twice-daily dosing on a continuous basis or twice-daily dosing for 3 consecutive days per week in patients with solid and hematologic malignancies. Seventy-three patients were treated with oral vorinostat, and the major dose-limiting toxicities were anorexia, dehydration, diarrhea, and fatigue. This study established that vorinostat could be administered chronically and safely using once-daily dosage (400 mg), twice-daily dosage (200 mg b.i.d.), and twice-daily dosage for 3 consecutive days (300 mg b.i.d.) every week (5). Vorinostat was shown to have good bioavailability and linear pharmacokinetics, and caused accumulation of acetylated histones in peripheral blood mononuclear cells, indicating inhibition of HDAC activity. Tumor regression and stable disease were observed in a wide range of patients with solid tumors and lymphomas. Major responses seen in 6 patients (1 complete response (CR) and 5 partial responses (PR)) occurred at the maximum tolerated dose and above; 5 of the 6 patients were treated on twice-daily regimens (5). This suggested that higher doses of vorinostat with more prolonged daily exposure might be required for tumor regression. Clinical activity was observed, with 1 CR and 1 PR in patients with diffuse large B-cell lymphoma, 2 PRs in patients with mesothelioma, and prolonged stable disease in thyroid cancer patients. The cumulative experience of the 39 patients with hematologic malignancies treated with oral or intravenous vorinostat included 5 patients with measurable disease responses, and 1 patient with a transformed small-cell lymphoma had a CR (6).

Zhang and colleagues (7) observed that vorinostat induced dose-dependent apoptosis in three cutaneous T-cell lymphoma (CTCL) cell lines and peripheral lymphocytes in patients with CTCL. Their data suggested that induction of malignant T-cell apoptosis and modulation of acetylated histones, p21WAF1, Stat6, and caspase-3 might underlie the therapeutic action of vorinostat in patients with CTCL (7). An early phase I study with the cyclic tetrapeptide HDACi, depsipeptide, demonstrated clinical activity in patients with CTCL (8). Based on these data, Duvic and colleagues performed a multiarm phase II study with vorinostat in patients with CTCL (9). Thirty-three patients were randomized to one of three dose regimens of vorinostat: (i) 400 mg daily; (ii) 300 mg for 3 days with 4-day rest; and (iii) 300 mg twice daily for 14 days with 7-day rest followed by 200 mg twice a day. CTCL patients were heavily pretreated with a median of 5 prior regimens. Eight patients (24.2%) were reported to have a PR, with median time to
progression of 30.2 weeks, and an impressive 45% of the patients with baseline pruritus had symptomatic relief. This study also confirmed that the 400-mg daily dose of vorinostat had the most favorable toxicity profile for future studies. The pivotal study for vorinostat was a large multicenter phase II study involving 18 centers in the United States and Canada that enrolled 74 patients with stage IB or more advanced CTCL (10). Objective responses were observed in 30% of the patients, and the median time to tumor progression was 202 days. The adverse event profile was similar to that reported in prior studies. Overall, the objective tumor regression and duration of response, coupled with the improvement in symptoms, were comparable with the results with other FDA-approved CTCL therapies: bexarotene and denileukin diftitox. Based on the cumulative clinical activity and acceptable toxicity profile, on October 6, 2006, the FDA approved vorinostat for the treatment of CTCL in patients with progressive, persistent, or recurrent disease on or following two systemic therapies (11).

The encouraging success in CTCL launched multiple studies with vorinostat as a single agent and in combination therapy in patients with hematologic and solid tumor malignancies. Response proportions similar to those seen in CTCL have been reported in patients with non-Hodgkin and mantle cell lymphoma and follow-up studies are ongoing (12). Unfortunately, the same clinical activity as a single agent or in combination with chemotherapy has only shown very limited clinical activity in patients with solid tumor malignancies (non–small cell lung cancer, metastatic radiiodine-refractory thyroid cancer, metastatic breast cancer, head and neck cancer, platinum-refractory ovarian or primary peritoneal carcinoma; ref. 13). Several combination studies that evaluated vorinostat with 5-fluorouracil/leucovorin in refractory colorectal cancer; bortezomib plus vorinostat in glioblastoma; vorinostat in combination with carboplatin and paclitaxel in patients with advanced non–small cell lung cancer also had disappointing results (13). Vorinostat in addition to tamoxifen for the treatment of patients with hormone therapy–resistant breast cancer did show an objective response rate of 19%, and the clinical benefit rate was 40% with a median duration of response of 10.3 weeks (13).

Overall, the data have not supported the approval of vorinostat for the treatment of additional malignancies. While this is disappointing, the clinical introduction of vorinostat 12 years ago ushered in a new era of research and discovery for epigenetic therapy. The clinical experience with vorinostat and other HDACis has shown that these drugs can be administered safely to patients; these agents can achieve intratumoral drug concentrations that cause accumulation of acetylated histones (a biologic effect); and in selected patients, clinical benefit has been observed in hematologic and solid tumor malignancies. However, the studies with vorinostat and other epigenetic-based therapies have highlighted multiple challenges for the development of these agents. Critical to the use of these agents is the identification of patient selection biomarkers for subsets of patients who have benefited from treatment. While several studies have suggested patient selection biomarkers, they have not yet been fully realized and implemented in the postapproval setting. In addition, it is critical to continue to develop the tools for drug discovery in this area, including diverse chemistry libraries to enable the development of next-generation agents and predictive model systems that reflect the epigenetic diversity of human tumors (12, 14). In addition, an increased understanding of the role of acetylation on histones and nonhistone proteins will improve our ability to use these inhibitors in cancer and potentially expand their use beyond cancer. Vorinostat has helped open the door for development of the next generation of HDACis that are now under evaluation in the clinic, such as the HDAC6 selective inhibitor ACY-1215 and novel sirtuin modulators, which will further move forward our understanding of epigenetic therapies (15, 16).

Disclosure of Potential Conflicts of Interest
V.M. Richon is an employee of and has ownership interest (including patents) in Epizyme, and reports receiving royalties from Memorial Sloan Kettering Cancer Center for a vorinostat composition of matter patent that is licensed to Aton Pharma, which was acquired by Merck. No potential conflicts of interest were disclosed by the other authors.

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Received February 8, 2015; revised March 16, 2015; accepted March 16, 2015; published online May 15, 2015.

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www.aacrjournals.org
Clin Cancer Res; 21(10) May 15, 2015
CCR 20th Anniversary Commentary: Vorinostat — Gateway to Epigenetic Therapy

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