LEUKEMIA & LYMPHOMA, 2016
VOL. 57, NO. 8, 1755–1765
http://dx.doi.org/10.3109/10428194.2016.1160082

Taylor & Francis
Taylor & Francis Group

REVIEW

Use of class I histone deacetylase inhibitor romidepsin in combination regimens

Adam Petrich[a] and Chadi Nabhan[b]

[a]Division of Hematology/Oncology, Northwestern University, Chicago, IL, USA; [b]Section of Hematology and Oncology, The University of Chicago, Chicago, IL, USA

ABSTRACT

Histone deacetylase (HDAC) inhibitors are epigenetic-modifying agents that have shown promise as anticancer therapies. Several HDAC inhibitors have been approved by the US Food and Drug Administration (FDA) as single-agent therapies to treat T-cell lymphoma. The synergistic combination of HDAC inhibitors with other anticancer agents has the potential to constitute treatment regimens with enhanced efficacy. Romidepsin is a structurally unique, potent, bicyclic class 1 selective HDAC inhibitor approved by the FDA for the treatment of patients with peripheral T-cell lymphoma who have had at least 1 prior therapy and patients with cutaneous T-cell lymphoma who have had at least 1 prior systemic therapy. Here, we review data that support the use of romidepsin in combination with other anticancer agents for the treatment of various malignancies. Promising results have emerged from early clinical studies, supporting the potential for romidepsin combination regimens to constitute safe and effective treatments for cancer.

ARTICLE HISTORY
Received 21 December 2015
Revised 11 February 2016
Accepted 21 February 2016

KEYWORDS
Combination therapy; epigenetics; histone deacetylase inhibitor

Introduction

In eukaryotic cell nuclei, genomic DNA is assembled onto histone proteins, which aid in packaging into nucleosomes, the repeating units of chromatin.[1] Histones undergo a wide variety of modifications that have significant effects on gene expression, including acetylation, methylation, phosphorylation, and ubiquitination.[2] Histone acetylation by histone acetyltransferases (HATs) leads to a more 'open' chromatin conformation, favoring transcription factor binding and gene transcription, while removal of acetyl groups by histone deacetylases (HDACs) results in tighter histone–DNA interactions and inhibition of transcription.[3] The opposing actions of HDACs and HATs also have various nonhistone substrates where acetylation status regulates activity, such as transcription factors and proteins involved in cell growth and differentiation.[4,5] Equilibrium between HAT and HDAC activity is needed for normal cell growth and function,[6] and perturbation of that equilibrium due to aberrant expression, function, and/or alteration of HDAC genes has been associated with various cancers.[4,5]

Human HDACs are divided into 4 classes (I–IV).[3] Classes I, II, and IV HDACs are zinc-dependent and the targets of HDAC inhibitors in clinical development.[4] Class III HDACs (sirtuins 1-7) are NAD + dependent and unaffected by current HDAC inhibitors.[5] Inhibition of HDACs prevents removal of acetyl groups from histone and nonhistone proteins, which allows DNA to remain transcriptionally active and maintains protein function.[5] Although pathways have not been well elucidated, HDAC inhibition in cancer cells is associated with various downstream effects, including enhanced cell death, cellular differentiation, and inhibition of angiogenesis and cell migration/motility.[3,4]

Several HDAC inhibitors with varying structural class, specificity, and potency are under investigation as anticancer agents.[3] Three HDAC inhibitors are currently approved by the US Food and Drug Administration (FDA) for the treatment of T-cell lymphoma (TCL). Intravenous (IV) bicyclic peptide class-I selective HDAC inhibitor romidepsin (Istodax, Celgene Corporation) is approved for both the treatment of cutaneous TCL (CTCL) in patients who have received at least 1 prior systemic therapy and the treatment of peripheral TCL (PTCL) in patients who have received at least 1 prior therapy.[4,7] Oral hydroxamate pan-HDAC inhibitor vorinostat (Zolinza, Merck & Co Inc.) is approved for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent

CONTACT Adam Petrich adampetrich@gmail.com Division of Hematology/Oncology, Northwestern University, 303 E Superior, Chicago, IL 60611, USA

disease on or following 2 systemic therapies.[4,8] The IV hydroxamate pan-HDAC inhibitor belinostat (Beleodaq, Spectrum Pharmaceuticals Inc.) is approved for the treatment of patients with relapsed or refractory PTCL.[4,9] Recently, the oral class I/II-specific hydroxamate HDAC inhibitor panobinostat (Farydak, Novartis Pharmaceuticals Corporation), in combination with bortezomib and dexamethasone, was approved by the FDA for the treatment of patients with multiple myeloma (MM) who have received ≥ 2 prior regimens (including bortezomib and an immunomodulatory agent).[4,10]

Single-agent romidepsin in T-cell lymphoma

TCLs (broadly classified PTCLs and CTCLs) are a heterogeneous group of uncommon non-Hodgkin lymphomas (NHL).[11] PTCLs are a diverse group of aggressive malignancies with poor prognosis for patients with most subtypes.[12] Most patients receive multiagent cytotoxic chemotherapy as front-line treatment; although most patients respond, prolonged remissions are rare.[11,13,14] Durable responses are particularly uncommon in patients with relapsed/refractory PTCL, and such patients face a particularly poor prognosis.[15]

CTCLs primarily present in the skin,[16] commonly with pruritus,[17] but can progress to systemic involvement.[16] Patients with early-stage disease are typically treated with skin-directed therapies,[11,18] and systemic treatments are usually delayed in those with particularly aggressive disease, or until patients have failed multiple skin-directed therapies. In some patients, disease remains restricted to the skin for many years, while in others it will progress more rapidly to systemic disease.[18,19] Those with rapid progression typically face a poor prognosis.[20] For patients with systemic disease, treatment strategies generally incorporate novel/biologic agents; cytotoxic chemotherapy (including combinations) is reserved for patients whose disease fails to respond or progresses after exposure to other systemic therapies. Skin-directed and systemic therapies may also be used in tandem.[11]

Phase I studies examined the safety and efficacy of romidepsin in advanced hematologic cancer and solid tumors.[21–23] All 4 patients with TCL enrolled in phase I studies had a clinical response: partial response (PR) in 3 patients with CTCL, complete response (CR) in 1 patient with PTCL.[22] These responses led to the initiation of a phase II trial from the National Cancer Institute (NCI) in relapsed/refractory PTCL and CTCL,[24,25] results from which supported the approvals that were primarily based on later pivotal phase II studies in each indication. In the pivotal phase II study of romidepsin in patients with relapsed/refractory PTCL who had ≥ 1 prior therapy ($N = 131$),[26] the ORR was 25%, including 15% with confirmed/unconfirmed CR (CR/CRu).[27] The median duration of response (DOR) for all responders was 28 months, and 10 of 19 patients who achieved CR/CRu had responses ≥ 12 months.[27] The longest response in the study was ongoing at 56+ months in a patient with AITL; including this patient, 4 of 5 patients with AITL who achieved CR/CRu were ongoing in response for >3 years and ultimately received maintenance dosing.[28] The study protocol was amended to allow for (but not mandate) maintenance dosing as a result of prolonged treatment in some patients. Patients who were treated for ≥ 12 cycles could receive maintenance dosing of twice per cycle; patients who received dosing of twice per cycle for ≥ 6 cycles and through cycle 24 could receive dosing of once per cycle.[27] The median progression-free and overall survival (PFS, OS) were 4 months and 11.3 months, respectively.[27]

In the pivotal phase II study of romidepsin in patients with relapsed/refractory CTCL who had ≥ 1 prior systemic therapy ($N = 96$),[29] ORR was 34% (33/96), including 6% with CR.[29] Responses were observed across disease compartments (skin, lymph nodes, blood). The median DOR was 15.0 months, with the longest response ongoing at 19.8+ months.[29] Concomitant anti-itch treatments such as steroids or antihistamines were not allowed to isolate the impact of romidepsin on pruritus, and 60 of 65 patients (92%) with moderate to severe pruritus at baseline (≥ 30 mm on a 100-mm visual analog scale) reported a reduction in their pruritus.[29,30] A clinically meaningful reduction in pruritus ($\geq$30-mm decrease or score of 0 for 2 consecutive cycles) was reported in 43% of patients with moderate to severe pruritus at baseline, including both objective responders (17/26, 65%) and nonresponders (11/39, 28%).[29,30]

Gastrointestinal toxicities and asthenic conditions were the most common romidepsin-related adverse events (AEs) in phase II studies of patients with PTCL and CTCL; they were primarily grade 1/2 and rarely resulted in discontinuation.[7,24–27,29,31] In the pivotal studies, grade ≥ 3 AEs reported in $\geq$5% of patients were thrombocytopenia (24%), neutropenia (20%), infections (all types pooled, 19%), anemia (11%), asthenia/fatigue (8%), leukopenia (6%), pyrexia (5%), vomiting (5%) in patients with PTCL, and infections (all types pooled, 11%), and asthenia/fatigue (8%) in patients with CTCL.[7] Hematologic AEs and grade ≥ 3 infections were more common in patients with PTCL vs. CTCL and likely related to prior myelosuppressive chemotherapy and bone

marrow disease. The majority of infections reported with romidepsin treatment were not drug-related, and thrombocytopenia was generally transient and not cumulative with continued treatment.[31] The incidences of grade ≥3 AEs and discontinuations reported were highest during cycles 1–2 of romidepsin treatment and declined thereafter.[31] No cumulative toxicities were reported with long-term treatment; most patients could remain on romidepsin for as long as they were benefiting clinically.[7,24,27,29,31]

There were early concerns regarding the cardiac safety of romidepsin. In a phase I study, reversible low-grade electrocardiogram changes and dysrhythmias were reported – first observed with romidepsin 3.5 mg/m^2, the lowest dose at which prophylactic antiemetics were also routinely administered [21]; commonly used antiemetics (e.g. ondansetron) are known to prolong the QT interval.[32] In phase II studies of romidepsin, patients with significant cardiac disease were excluded, and enrolled patients had routine cardiac monitoring [33] as well as electrolyte supplementation as needed, because hypokalemia and hypomagnesemia may cause electrocardiogram abnormalities.[33,34] Results from a thorough postmarketing cardiac study in patients with advanced malignancies showed that despite the use of QT-prolonging antiemetics, romidepsin treatment did not significantly prolong corrected QT (QTc), even at supratherapeutic doses.[35] The reported increases in QTc were exaggerated due to concomitant antiemetics and transient increases in heart rate. To date, romidepsin has not been associated with myocardial damage or impaired cardiac function in any study.[7] The durable clinical activity and long-term tolerability of romidepsin make it a promising candidate for combination therapies.

Combination studies with romidepsin

Although single-agent HDAC inhibitors, including romidepsin, have demonstrated limited activity in solid tumors, investigators hoped that due to their pleiotropic actions they may have utility in combination regimens. Early combination studies, which focused primarily on solid tumors and utilized agents that had single-agent activity and preclinical synergy with romidepsin, have been disappointing [Table 1]. More recent studies, primarily in hematologic malignancies, have combined 2 agents with single-agent activity in certain disease states [Tables 2 and 3].

Romidepsin in combination with other agents with single-agent activity in TCL

Pralatrexate

The folate analog pralatrexate is approved by the FDA for the treatment of patients with relapsed/refractory PTCL.[36] In a murine model of TCL, pralatrexate + romidepsin exhibited enhanced efficacy compared with either drug alone.[37] A phase I/IIa study of romidepsin + pralatrexate in relapsed/refractory lymphoid malignancies ($N = 93$; NCT01947140) is ongoing.

Lenalidomide

The immunomodulatory agent lenalidomide is approved by the FDA for the treatment of MM in combination with dexamethasone, transfusion-dependent anemia due to lower-risk del5q myelodysplastic syndromes (MDS), and NHL subtype mantle cell lymphoma (MCL) that has relapsed or progressed after 2 prior therapies (including bortezomib).[38] Lenalidomide has also shown activity in various other NHL subtypes,[39–41] and there was synergy with romidepsin and lenalidomide in TCL cell lines.[42,43]

A phase I/II study of romidepsin + lenalidomide has been initiated in relapsed/refractory lymphomas and MM ($N = 19$), although only patients with lymphoma have been enrolled thus far.[44] In this study, romidepsin is to be given on days 1, 8, and 15 and oral lenalidomide on days 1–21 of 28-day cycles in a standard 3 + 3 dose-escalation scheme, in the following 4 cohorts: romidepsin 8 mg/m^2 + lenalidomide 15 mg, romidepsin 8 mg/m^2 + lenalidomide 25 mg, romidepsin 10 mg/m^2 + lenalidomide 25 mg, and romidepsin 14 mg/m^2 + lenalidomide 25 mg. Of 15 patients, 2 experienced DLTs of grade 4 pneumonia and grade 3 thrombocytopenia. No cumulative toxicities were reported, and the ORR was 54% (7/13), including 4 of 6 patients (67%) with TCL.[44] In the phase II portion of the study, the ORR was 53% (10/19), including 5 of 10 patients (50%) with PTCL and 5 of 9 patients (56%) with CTCL. Of 21 patients with TCL who were treated, 71% had a grade ≥3 AE, the most common (≥10%) of which were neutropenia (48%), thrombocytopenia (38%), anemia (33%), and electrolyte abnormalities (43%).[45] A separate phase I/IIa study of romidepsin + lenalidomide in patients with relapsed/refractory Hodgkin lymphoma, mature TCL, or MM ($N = 100$; NCT01742793) is ongoing. Patients with disease refractory to prior HDAC inhibitor monotherapy are allowed to enroll. A separate phase II study of romidepsin + lenalidomide in untreated PTCL ($N = 35$; NCT02232516) is also ongoing.

Table 1. Key combination studies with romidepsin in solid tumors.

In combination with	Clinical trial	Rationale	Key reported efficacy data
Gemcitabine (nucleoside analog)	Ph 1 in solid tumors in which gemcitabine had shown clinical activity ($N = 36$; NCT00379639) [87]	• Clinical activity (FDA approval) of single-agent gemcitabine [88] • Preclinical activity of single-agent romidepsin in various solid cancer cells [89–95] and synergy with gemcitabine [96]	• Primarily enrolled pts with pancreatic, breast, or lung cancers • 27 evaluable pts: 7% PR (1 ovarian, 1 breast), 52% SD [87]
Erlotinib (EGFR tyrosine kinase inhibitor)	Ph 1 in previously treated advanced NSCLC ($N = 15$; NCT01302808) [97]	• Clinical activity of single-agent erlotinib [98] • Preclinical activity of single-agent romidepsin [92–94] and synergy with erlotinib [99]	• 9 evaluable pts: no responses, 67% SD [97]
Flavopiridol (cyclin-dependent kinase inhibitor)	Ph 1 in cancers of the lungs, esophagus, pleura, thymus, or mediastinum ($N = 23$; NCT00094978)	• Abrogation of romidepsin-mediated p21/WAF1 upregulation enhances apoptosis [100] • Flavopiridol inhibits p21/WAF1 expression,[101] has preclinical activity,[102] and enhanced preclinical activity of romidepsin [103]	• Trial terminated without publication of data
Nab-paclitaxel (paclitaxel [microtubule inhibitor] protein bound particles)	Ph 1/2 in metastatic inflammatory breast cancer ($N = 47$; NCT01938833)	• Clinical activity (FDA approval) of single-agent nab-paclitaxel [104] • Preclinical activity of single-agent romidepsin [90,91,105] and synergy with paclitaxel [105]	• NR, currently enrolling
Cisplatin (DNA-damaging agent)	Ph 1/2 in locally recurrent or metastatic triple-negative breast cancer ($N = 54$; NCT02393794)	• Clinical activity of single-agent cisplatin [106] • Preclinical activity of single-agent romidepsin and enhancement of preclinical activity of cisplatin [107]	• NR, currently enrolling
Decitabine (hypomethylator)	Ph 1 (± celecoxib) in pulmonary and pleural malignancies ($N = 34$; NCT00037817)	• Different components of epigenetic machinery are known to interact [53,54] • Preclinical synergy of decitabine + romidepsin [56–59]	• Study complete, but data not reported to date
CC-486 (oral azacitidine; hypomethylator)	Ph 1 in advanced solid tumors ($N = 39$; NCT01537744)	• Preclinical synergy of decitabine + romidepsin [56–59] shows promise for the 2 drug classes • Oral administration of hypomethylator allows for investigation of varying dosing regimens	• NR, currently enrolling

EGFR: epidermal growth factor receptor; FDA: US Food & Drug Administration; NR: not reported; NSCLC: non-small cell lung cancer; Ph: phase; PR: partial response; pt: patient; SD: stable disease.

Lenalidomide has also been shown to have clinical activity in indolent B-cell lymphomas (BCLs) in combination with the anti-CD20 antibody rituximab,[46] and the combination also overcomes prior resistance to rituximab in patients with BCLs.[47] Decreased expression of CD20 is a major mechanism underlying resistance to rituximab, and romidepsin was shown to increase CD20 expression in BCL cell lines.[48] In addition, romidepsin + rituximab synergistically retarded cell growth in mouse lymphoma models.[48] A phase I/II study of romidepsin + lenalidomide + rituximab in relapsed/refractory BCLs ($N = 56$, NCT02281279) is not yet enrolling.

Alisertib

The aurora kinase inhibitor alisertib has shown promising single-agent results in phase II studies in TCL.[49,50] Romidepsin + alisertib were shown to be highly synergistic in TCL, but not BCL, cell lines; no synergy was shown for alisertib + pralatrexate or proteasome inhibitors in TCL or BCL.[51] In a phase I study of romidepsin + alisertib in relapsed/refractory aggressive BCLs and TCLs ($N = 9$), oral alisertib is given on days 1–7 and IV romidepsin on days 1 and 8 of 21-day cycles in the following cohorts: romidepsin 8 mg/m^2 + alisertib 20 mg twice daily (BID), romidepsin 10 mg/m^2 + alisertib 20 mg BID, romidepsin 10 mg/m^2 + alisertib 40 mg BID, romidepsin 12 mg/m^2 + alisertib 40 mg BID, and romidepsin 14 mg/m^2 + alisertib 40 mg BID.[52] Of 9 enrolled patients, grade 3/4 toxicities were most commonly neutropenia (45%), thrombocytopenia (45%), and anemia (20%). In 8 evaluable patients, best responses are 1 CR and 1 SD, both in patients with PTCL.

Romidepsin in combination with another epigenetic-modifying therapy

Different components of epigenetic machinery are known to interact – for example, hypermethylated

Table 2. Key reporting studies with romidepsin in hematologic malignancies.

In combination with	Clinical trial	Key reported efficacy data
Lenalidomide (immunomodulatory agent)	Ph 1/2 in relapsed/refractory lymphomas and MM ($N = 19$; NCT01755975) [44]	• Only pts with lymphoma enrolled thus far [44] • 54% ORR (7/13) including 67% (4/6) of those with TCL • Phase 2 portion will include expanded cohort of pts with TCL
Alisertib (aurora kinase inhibitor)	Ph 1 in R/R aggressive BCLs and TCLs ($N = 9$; NCT01897012) [52]	• In 8 pts, best responses of 1 CR and 1 SD (both in PTCL) [52]
CHOP (anthracycline-based chemotherapy)	Ph 1b/2 in previously untreated PTCL ($N = 37$; NCT01280526) [64]	• Of 35 evaluable pts, 69% ORR including 51% CR [64] • Median PFS and OS 21.3 mo and NR, respectively
ICE (chemotherapy)	Ph 1 in R/R PTCL ($N = 30$; NCT01590732) [67]	• Of 7 evaluable pts, 71% ORR (all CR) [67] • Median DOR 7.2 mo
Bortezomib (proteasome inhibitor)	Ph 1/2 + dexamethasone in R/R MM ($N = 25$; NCT00431990) [74]	• Of 25 evaluable pts, 72% ORR (2 CR, 7 VGPR, 6 PR, 3 MR) [74] • Median TTP 7.2 mo and median OS > 36 mo • Despite positive results, combination not pursued
	Ph 1 in CLL/SLL, indolent BCL, PTCL, and CTCL ($N = 18$, NCT00963274)[84]	• Of 18 evaluable pts, 1 PR (CLL) and 9 SD (6 CLL/SLL, 1 CTCL, 2 indolent BCL) [84]

BCL: B-cell lymphoma; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CLL: chronic lymphocytic leukemia; CR: complete response; CTCL: cutaneous T-cell lymphoma; DOR: duration of response; FDA: US Food & Drug Administration; HDACi: histone deacetylase inhibitor; ICE: ifosfamide + carboplatin + etoposide; MM: multiple myeloma; MR: minor response; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; Ph: phase; PR: partial response; pt: patient; PTCL: peripheral T-cell lymphoma; SD: stable disease; SLL: small lymphocytic lymphoma; TCL: T-cell lymphoma; TTP: time to treatment progression; VGPR: very good partial response.

Table 3. Key emerging studies with romidepsin in hematologic malignancies.

In combination with	Clinical trial
Pralatrexate (folate analog)	Ph 1/2a in R/R lymphoid malignancies ($N = 93$; NCT01947140)
Lenalidomide (immunomodulatory agent)	Ph 1/2a in R/R Hodgkin lymphoma, mature TCL, or MM ($N = 100$; NCT01742793) Ph 2 in untreated PTCL ($N = 35$; NCT02232516) Ph 1b/2a + carfilzomib in refractory BCLs and TCLs ($N = 25$; NCT02341014)[a] Ph 1/2 + rituximab in R/R BCLs ($N = 56$; NCT02281279)
Pomalidomide (immunomodulatory agent)	Ph 1/2 + dexamethasone in R/R MM ($N = 48$; NCT01979276)
Decitabine (hypomethylator)	Ph 1 in R/R leukemia, myeloproliferative disorders, or MDS ($N = 36$; NCT00114257)[b]
CC-486 (oral azacitidine; hypomethylator)	Ph 1/2 in R/R lymphoid malignancies ($N = 60$; NCT01998035)
CHOP (anthracycline-based chemotherapy)	Ph 3 (CHOP ± romidepsin) in previously untreated PTCL ($N = 420$; NCT01796002) [65]
CHOEP (anthracycline-based chemotherapy)	Ph 1/2 prior to SCT in young pts (18–65 y) with untreated nodal PTCLs ($N = 110$; NCT02223208)
Liposomal doxorubicin (anthracycline)	Ph 1 in R/R CTCL ($N = 24$; NCT01902225)
Gemcitabine (nucleoside analog)	Ph 2a in R/R PTCL ($N = 20$; NCT01822886)
GDP (gemcitabine-containing regimen)	Ph 1 in R/R PTCL or DLBCL ($N = 24$; NCT01846390)
GemOx + dexamethasone (gemcitabine-containing regimen)	Ph 1 in R/R PTCL, CTCL, and DLBCL ($N = 27$; NCT02181218)
Carfilzomib (proteasome inhibitor)	Ph 1 in CTCL ($N = 48$; NCT01738594) Ph 1b/2a + lenalidomide in refractory BCLs and TCLs ($N = 25$; NCT02341014)[a]
Radiation	Ph 1 + TLR agonist poly-ICLC in CTCL ($N = 24$; NCT02061449)

[a]This study is noted twice in table, in both the lenalidomide and carfilzomib sections.
[b]Study is listed as complete; however, no data have been reported to date.
BCL: B-cell lymphoma; CHOEP: CHOP + etoposide; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CTCL: cutaneous T-cell lymphoma; DLBCL: diffuse large B-cell lymphoma; FDA: US Food & Drug Administration; GDP: gemcitabine + dexamethasone + cisplatin; GemOx: gemcitabine + oxaliplatin; MDS: myelodysplastic syndromes; MM: multiple myeloma; Ph: phase; pt: patient; PTCL: peripheral T-cell lymphoma; R/R: relapsed/refractory; SCT: stem cell transplant; TCL: T-cell lymphoma; TLR: toll-like receptor.

DNA associates with transcriptionally repressive chromatin characterized by underacetylated histones,[53] and *in vitro* and *in vivo* synergy of DNA demethylation and HDAC inhibition has been shown for the re-expression of genes silenced in cancer.[53,54]

Hypomethylating agents

Decitabine is a hypomethylating agent approved by the FDA for the treatment of intermediate- and high-risk MDS.[55] Romidepsin + decitabine has shown preclinical synergy in various malignancies, including acute myeloid leukemia (AML), diffuse large BCL (DLBCL), and lung cancers.[56–59] In preclinical models of TCL, HDAC inhibitors (romidepsin, vorinostat, belinostat, panobinostat) were combined with hypomethylating agents (azacitidine, decitabine), and the deepest synergy was shown with romidepsin + decitabine.[60] In response, phase I studies of romidepsin + decitabine in relapsed/refractory leukemia, myeloproliferative

disorders, or MDS ($N = 36$; NCT00114257) and in pulmonary and pleural malignancies (±celecoxib; $N = 34$; NCT00037817), were initiated. Both studies are complete, but neither has reported safety or efficacy data. Newer studies have focused on CC-486 (oral azacitidine). Hypomethylating effects are cell-cycle dependent [61]; several cycles of DNA replication are required for DNA hypomethylation,[62] and extensive demethylation requires prolonged drug exposure.[63] Oral administration allows for alternative dosing, including extended dosing schedules, and enables long-term dosing, which allows for increased exposure to cycling malignant cells. A phase I/II study of romidepsin + CC-486 in relapsed/refractory lymphoid malignancies ($N = 60$; NCT01998035) and a phase I study of romidepsin + CC-486 in advanced solid tumors (expansion cohort in virally mediated cancers and liposarcoma, $N = 39$; NCT01537744) are ongoing.

Improving outcomes with current chemotherapy regimens

Current chemotherapy regimens used to treat TCL are not adequate. The activity of durable novel agents, such as romidepsin, in patients with relapsed or refractory TCL suggests that combination with chemotherapy has the potential to prolong remissions.

Anthracycline-based therapies

The majority of patients with PTCL receive anthracycline-based therapies (e.g. CHOP [cyclophosphamide + doxorubicin + vincristine + prednisone], CHOEP [CHOP ± etoposide]) in the first-line, based largely on prior success in the treatment of BCLs.[11,13] Most patients respond, but responses are typically brief and many patients experience rapid relapse.

Romidepsin + CHOP is being evaluated in a non-randomized dose-escalation (phase Ib) and dose-expansion (phase II) study in patients with previously untreated PTCL ($N = 37$).[64] In the phase Ib portion ($n = 18$), a standard 3 + 3 dose-escalation scheme was used, with eight 21-day cycles planned, including CHOP and romidepsin as a 3-hour infusion at 8, 10, or 12 mg/m^2 on days 1 and 8. Reported DLTs included syncope (without sequelae), neutropenia, hyponatremia/hypophosphatemia, pulmonary edema, and vomiting. Romidepsin 12 mg/m^2 was chosen for the phase II portion ($n = 19$). Grade ≥ 3 hematologic toxicity occurred in the majority of patients ($N = 37$), with most common nonhematologic events categorized as gastrointestinal, respiratory, or general conditions. Of 35 evaluable patients, the ORR was 69%, including 51% with CR. The median PFS and OS were 21.3 months and not reached, respectively. These phase Ib/II results led to initiation of a phase III study of CHOP vs. romidepsin + CHOP in previously untreated PTCL ($N = 420$; NCT01796002) which is ongoing.[65]

A separate phase I/II study of romidepsin + CHOEP prior to stem cell transplant in young patients (age 18–65 years) with untreated nodal PTCLs ($N = 110$; NCT02223208) is also ongoing. Single-agent liposomal doxorubicin is suggested for the treatment of relapsed/refractory CTCL,[11] and a phase I study of romidepsin + doxorubicin in relapsed/refractory CTCL ($N = 24$; NCT01902225) is ongoing.

ICE (ifosfamide + carboplatin + etoposide)

The chemotherapy regimen ICE is used as salvage therapy for patients with PTCL.[11,66] In a phase I study in relapsed/refractory PTCL, standard ICE is given with romidepsin 8, 10, or 12 mg/m^2 on days 1 and 4.[67] In the first 9 patients enrolled, DLTs included renal failure (associated with ifosfamide and etoposide) and thrombocytopenia. Five of 7 evaluable patients achieved a response (71%), which were all CR, and the median DOR was 7.2 months. Grade 3/4 thrombocytopenia and neutropenia were reported in 87% and 40% of treatment cycles administered, respectively.

Gemcitabine-containing regimens

Despite minimal clinical activity of the combination in solid tumors, romidepsin + gemcitabine is being studied in several trials underway in patients with PTCL. GDP (gemcitabine, dexamethasone, cisplatin) and GemOx (gemcitabine, oxaliplatin) are used as salvage regimens for patients with PTCL,[11] and phase I studies are ongoing in romidepsin + GemOx + dexamethasone for treating relapsed/refractory PTCL, CTCL, and DLBCL ($N = 27$; NCT02181218) and romidepsin + GDP for relapsed/refractory PTCL or DLBCL ($N = 24$; NCT01846390). Single-agent gemcitabine is currently used in patients with PTCL who are not candidates for high-dose therapy, as well as for patients with CTCL.[11] A phase IIa study of romidepsin + gemcitabine in relapsed/refractory PTCL ($N = 20$; NCT01822886) is ongoing.

Proteasome inhibitors

Bortezomib is a proteasome inhibitor approved for the treatment of MM and MCL.[68] Romidepsin was shown to induce apoptosis in MM cell lines and primary cells from MM patients,[69] and synergy between proteasome inhibitors and HDAC inhibitors has been

demonstrated in MM cells.[70–73] In a phase I/II study in patients with relapsed/refractory MM, bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) + dexamethasone (20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12) were combined with romidepsin (8–14 mg/m^2 on days 1, 8, and 15) in 28-day cycles ($N = 25$).[74] Reported DLTs included thrombocytopenia, febrile neutropenia, intracerebral hemorrhage, and bowel obstruction. The MTD of romidepsin was 10 mg/m^2. The most common grade ≥ 3 AE was thrombocytopenia (64%) and all-grade peripheral neuropathy was reported in 76% of patients (8% grade ≥ 3). The ORR was 72% (18 of 25 evaluable patients), including 2 patients with CR and 13 with PR (7 with very good PR). The median time to progression was 7.2 months, and the median OS was > 36 months. Despite these positive results, this combination was not investigated further, and the combination of panobinostat + bortezomib + dexamethasone was recently approved for the treatment of MM in patients who have received ≥ 2 prior regimens (including bortezomib and an immunomodulatory agent).[10] Prescribing information for the combination include black box warnings related to severe diarrhea and severe and fatal cardiac ischemic events.

Bortezomib was also shown to induce apoptosis in CLL cells.[75] In a phase II study of bortezomib 1-1.5 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles in CLL ($N = 22$), no objective responses were reported.[76] It was later shown that dietary flavonoids abundant in plasma inhibit bortezomib in patients with CLL.[77] Romidepsin showed selective cytotoxicity toward CLL cells vs. normal peripheral blood mononuclear cells,[78] as well as histone H3 and H4 acetylation, HDAC enzyme inhibition, and apoptosis in cultured CLL cells.[79] In a phase I study of romidepsin 13 mg/m^2 on days 1, 8, and 15 of 28-day cycles in CLL ($n = 10$), no objective responses were reported and most patients discontinued due to nausea.[80] Bortezomib + romidepsin (or belinostat) synergistically induced cell death in primary and cultured CLL cells.[81] Bortezomib is also a suggested salvage regimen for patients with PTCL who are not candidates for high-dose therapy,[11] and a phase II study demonstrated activity in relapsed/refractory CTCL.[82] Synergy was also shown for the HDAC inhibitor vorinostat + bortezomib in TCL cell lines.[83] In a phase I study, a standard 3 + 3 dose-escalation scheme was used to combine romidepsin (8 or 10 mg/m^2 on days 1, 8, and 15) + bortezomib (1.3 or 1.6 mg/m^2 on days 1, 8, and 15) in 28-day cycles in patients with chronic lymphocytic lymphoma (CLL) or small lymphocytic lymphoma (SLL), indolent BCL, PTCL, and CTCL ($N = 18$).[84] Three DLTs occurred (fatigue, chills, and vomiting; all grade 3), and the MTD was romidepsin 10 mg/m^2 + bortezomib 1.3 mg/m^2. Grade 4 drug-related neutropenia was reported in 17% of patients, and the most common drug-related grade 3 AEs were neutropenia, vomiting, and fatigue (each 11%). Best responses included 1 PR (CLL) and 9 SD (6 patients with CLL/SLL, 1 with CTCL, 2 with indolent BCL).[84]

Carfilzomib is a new-generation proteasome inhibitor associated with less peripheral neuropathy than bortezomib.[85] A phase I study of carfilzomib ± romidepsin in CTCL ($N = 48$; NCT01738594) and a phase Ib/IIa study of romidepsin + lenalidomide + carfilzomib in refractory BCLs and TCLs ($N = 25$; NCT02341014) are ongoing.

Radiation

Local radiation is a suggested treatment for skin lesions in patient with CTCL.[11] In 5 patients with advanced CTCL who received low-dose electron beam radiation and romidepsin, 4 demonstrated rapid and durable responses.[86] A phase I study of romidepsin + radiation + toll-like receptor agonist poly-ICLC in CTCL ($N = 24$; NCT02061449) is ongoing.

Discussion

The epigenetic modifier romidepsin is a structurally unique, potent, bicyclic class 1 selective HDAC inhibitor. As a single agent, romidepsin delivers durable responses with manageable toxicity in patients with TCL. In addition to its pleiotropic activities, these attributes make romidepsin a promising agent for combination regimens. Early trials in solid tumors based on preclinical synergy with romidepsin and single-agent activity of the other agent were disappointing, demonstrating that preclinical synergy does not always translate to improved clinical outcomes. More recent studies have focused on combining romidepsin with several agents with single-agent activity and preclinical synergy, or combining it with currently used chemotherapy regimens to improve results. We are awaiting data from many of these more recent studies; however, encouraging activity has been seen in combination studies to date.

Acknowledgements

The authors take full responsibility for the content of this manuscript, but thank Stacey Rose, PhD, and William Ho, PhD (MediTech Media), for providing medical editorial

assistance. Financial support for medical editorial assistance was provided by Celgene Corporation.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http: http://dx.doi.org/10.3109/10428194.2016.1160082.

References

[1] Sajan SA, Hawkins RD. Methods for identifying higher-order chromatin structure. Annu Rev Genomics Hum Genet. 2012;13:59–82.

[2] Kouzarides T. Chromatin modifications and their function. Cell. 2007;128:693–705.

[3] Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. 2006;5:769–784.

[4] New M, Olzscha H, La Thangue NB. HDAC inhibitor-based therapies: can we interpret the code? Mol Oncol. 2012;6:637–656.

[5] Marsoni S, Damia G, Camboni G. A work in progress: the clinical development of histone deacetylase inhibitors. Epigenetics 2008;3:164–171.

[6] Lehrmann H, Pritchard LL, Harel-Bellan A. Histone acetyltransferases and deacetylases in the control of cell proliferation and differentiation. Adv Cancer Res. 2002;86:41–65.

[7] ISTODAX (romidepsin) [package insert]. Summit, NJ: Celgene Corporation; 2014. [cited 2016 Apr 15]. Available from: http://www.istodax.com/wp-content/uploads/ISTODAX_PackageInsert.pdf.

[8] Zolinza (vorinostat) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2015. [cited 2016 Apr 15]. Available from: https://www.merck.com/product/usa/pi_circulars/z/zolinza/zolinza_pi.pdf.

[9] Beleodaq (belinostat) [package insert]. Irvine, CA: Spectrum Pharmaceuticals; 2014. [cited 2016 Apr 15]. Available from: http://www.sppirx.com/downloads/140703_final-beleodaq-pi-pt-info.pdf.

[10] Farydak (panobinostat) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2016. [cited 2016 Apr 15]. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/farydak.pdf.

[11] NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas V.2.2016. [cited 2016 Apr 15]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[12] Foss FM, Zinzani PL, Vose JM, et al. Peripheral T-cell lymphoma. Blood 2011;117:6756–6767.

[13] Horwitz SM. Management of peripheral T-cell non-Hodgkin's lymphoma. Curr Opin Oncol. 2007;19:438–443.

[14] Foss FM, Carson KR, Pinter-Brown L, et al. Comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE): first detailed report of primary treatment. Blood. 2012;120:Abstract 1614.

[15] Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013;31:1970–1976.

[16] Jawed SI, Myskowski PL, Horwitz S, et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol. 2014;70:205.e1–205.e16.

[17] Demierre M. Mycosis fungoides and sezary syndrome: the burden of pruritus. Commun Oncol. 2010;7:399–404.

[18] Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sézary syndrome. Blood. 2009;114:4337–4353.

[19] Parker SR, Bradley B. Treatment of cutaneous T-cell lymphoma/mycosis fungoides. Dermatol Nurs. 2006;18:566–570, 573–575. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17286158.

[20] Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised international society for cutaneous lymphomas/european organisation for research and treatment of cancer staging proposal. J Clin Oncol. 2010;28:4730–4739.

[21] Sandor V, Bakke S, Robey RW, et al. Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res. 2002;8:718–728.

[22] Piekarz RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. Blood. 2001;98:2865–2868.

[23] Marshall JL, Rizvi N, Kauh J, et al. A phase I trial of depsipeptide (FR901228) in patients with advanced cancer. J Exp Ther Oncol. 2002;2:325–332.

[24] Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2009;27:5410–5417.

[25] Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood. 2011;117:5827–5834.

[26] Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30:631–636.

[27] Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol. 2014;7:11. Available from: http://jhoonline.biomedcentral.com/articles/10.1186/1756-8722-7-11.

[28] Pro B, Horwitz SM, Prince HM, et al. Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma (AITL). Blood. 2014;124:Abstract 1742.

[29] Whittaker SJ, Demierre M, Kim EJ, et al. Final results from a multicenter, international, pivotal study of

romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol. 2010;28:4485–4491.
[30] Kim YH, Demierre MF, Kim EJ, et al. Clinically meaningful reduction in pruritus in patients with cutaneous T-cell lymphoma treated with romidepsin. Leuk Lymphoma. 2013;54:284–289.
[31] Foss F, Coiffier B, Horwitz S, et al. Tolerability to romidepsin in patients with relapsed/refractory T-cell lymphoma. Biomark Res. 2014;2:167771-2-16. eCollection 2014.
[32] Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine-3 receptor antagonists. Ann Pharmacother. 2003;37:1276–1286.
[33] Piekarz RL, Frye AR, Wright JJ, et al. Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. Clin Cancer Res. 2006;12:3762–3773.
[34] Cabell C, Bates S, Piekarz R, et al. Systematic assessment of potential cardiac effects of the novel histone deacetylase (HDAC) inhibitor romidepsin. Blood. 2009;114:Abstract 3709.
[35] Sager PT, Balser B, Wolfson J, et al. Electrocardiographic effects of class 1 selective histone deacetyalse inhibitor romidepsin. Cancer Med. 2015;4:1178–1185.
[36] Folotyn (pralatrexate injection) [package insert]. Westminster, CO: Allos Therapeutics, Inc; 2012. [cited 2016 Apr 15]. Available from: http://www.folotyn.com/downloads/2012_05_folotyn_FPI.pdf.
[37] Jain S, Jirau-Serrano X, Zullo KM, et al. Preclinical pharmacologic evaluation of pralatrexate and romidepsin confirms potent synergy of the combination in a murine model of human T-cell lymphoma. Clin Cancer Res. 2015;21:2096–2106.
[38] Revlimid (lenalidomide) [package insert]. Summit, NJ: Celgene Corporation; 2015. [cited 2016 Apr 15]. Available from: http://www.revlimid.com/wp-content/uploads/full-prescribing-information.pdf.
[39] Witzig TE, Vose JM, Moore TD, et al. Results from a phase II study of lenalidomide oral monotherapy in relapsed/refractory indolent non-Hodgkin's lymphoma. Blood. 2007;110:Abstract 2560.
[40] Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's lymphoma. J Clin Oncol. 2009;27:5404–5409.
[41] Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008;26:4952–4957.
[42] Cosenza M, Civallero M, Fiorcari S, et al. Romidepsin synergizes with lenalidomide in T cell lymphoma cell lines by increasing reactive oxygen species and modulating PI3K/AKT and MAPK/ERK signaling pathways. Blood. 2014;124:Abstract 1778.
[43] Cosenza M, Civallero M, Fiorcari S, et al. Romidepsin and lenalidomide show a synergistic effect in T-cell lymphoma cell lines. Blood. 213:122:Abstract 5148.
[44] Lunning MA, Ruan J, Nair S, et al. A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relaped/refractory lymphoma and myeloma: phase 1 results. J Clin Oncol. 2014;32:Abstract 8582.
[45] Mehta-Shah N, Lunning MA, Ruan J, et al. A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma. Hematol Oncol. 2015;33:Abstract 016.
[46] Fowler NH, Davis RE, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol. 2014;15:1311–1318.
[47] Chong EA, Ahmadi T, Aqui NA, et al. Combination of lenalidomide and rituximab overcomes rituximab resistance in patients with indolent B-cell and mantle cell lymphomas. Clin Cancer Res. 2015;21:1835–1842.
[48] Shimizu R, Kikuchi J, Wada T, et al. HDAC inhibitors augment cytotoxic activity of rituximab by upregulating CD20 expression on lymphoma cells. Leukemia. 2010;24:1760–1768.
[49] Friedberg J, Mahadevan D, Jung J, et al. Phase 2 trial of alisertib (MLN8237), an investigational, potent inhibitor of aurora A kinase (AAK), in patients (pts) with aggressive B- and T-cell non-Hodgkin lymphoma (NHL). Blood. 2011;118:Abstract 95.
[50] Barr PM, Li H, Spier CM, et al. U.S. intergroup phase II trial (SWOG 1108) of alisertib, an investigational aurora A kinase (AAK) inhibitor, in patients with peripheral T-cell lymphoma (PTCL; NCT01466881). J Clin Oncol. 2014;5s:Abstract 8523.
[51] Zullo K, Guo Y, Cooke L, et al. The investigational aurora A kinase inhibitor alisertib exhibits broad activity in preclinical models of T-cell lymphoma and is highly synergistic with romidepsin. Blood. 2014;124:Abstract 4493.
[52] Fanale MA, Hagemeister FB, Fayad L, et al. A phase I trial of alisertib plus romidepsin for relapsed/refractroy aggressive B- and T-cell lymphomas. Blood. 2014;124:Abstract 1744.
[53] Cameron EE, Bachman KE, Myohanen S, et al. Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer. Nat Genet. 1999;21:103–107.
[54] Belinsky SA, Klinge DM, Stidley CA, et al. Inhibition of DNA methylation and histone deacetylation prevents murine lung cancer. Cancer Res. 2003;63:7089–7093.
[55] Dacogen (decitabine) [package insert]. Dublin, CA: Astex Pharmaceuticals, Inc; 2014. [cited 2016 Apr 15]. Available from: http://otsuka-us.com/products/Documents/DACOGEN.PI.pdf.
[56] Zhu WG, Lakshmanan RR, Beal MD, et al. DNA methyltransferase inhibition enhances apoptosis induced by histone deacetylase inhibitors. Cancer Res. 2001;61:1327–1333.
[57] Klisovic MI, Maghraby EA, Parthun MR, et al. Depsipeptide (FR 901228) promotes histone acetylation, gene transcription, apoptosis and its activity is enhanced by DNA methyltransferase inhibitors in AML1/ETO-positive leukemic cells. Leukemia. 2003;17:350–358.
[58] Shaker S, Bernstein M, Momparler LF, et al. Preclinical evaluation of antineoplastic activity of inhibitors of DNA methylation (5-aza-2′-deoxycytidine) and histone deacetylation (trichostatin A, depsipeptide) in

combination against myeloid leukemic cells. Leuk Res. 2003;27:437–444.
[59] Kalac M, Scotto L, Marchi E, et al. HDAC inhibitors and decitabine are highly synergistic and associated with unique gene-expression and epigenetic profiles in models of DLBCL. Blood. 2011;118:5506–5516.
[60] Marchi E, Zullo KM, Amengual JE, et al. The combination of hypomethylating agents and histone deacetylase inhibitors produce marked synergy in preclinical models of T-cell lymphoma. Br J Haematol. 2015; 171:215–226.
[61] Palii SS, Van Emburgh BO, Sankpal UT, et al. DNA methylation inhibitor 5-aza-2′-deoxycytidine induces reversible genome-wide DNA damage that is distinctly influenced by DNA methyltransferases 1 and 3B. Mol Cell Biol. 2008;28:752–771.
[62] Santini V, Kantarjian HM, Issa JP. Changes in DNA methylation in neoplasia: pathophysiology and therapeutic implications. Ann Intern Med. 2001;134:573–586.
[63] Lu LJ, Randerath K. Long term instability and molecular mechanism of 5-azacytidine-induced DNA hypomethylation in normal and neoplastic tissues in vivo. Mol Pharmacol. 1984;26:594–603.
[64] Dupuis J, Morschhauser F, Ghesquieres H, et al. Combination of romidepsin with cyclosphosphamide, doxorubicin, vinrcristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: a non-randomised, phase 1b/2 study. Lancet Haematol. 2015;2:e160–e165.
[65] Delarue R, Zinzani PL, Hertzberg MS, et al. ROCHOP study: a phase III randomized study of CHOP compared to romidepsin-CHOP in untreated peripheral T-cell lymphoma. J Clin Oncol. 2013;31:Abstract TPS8616.
[66] Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003;14:i5–i10.
[67] Chihara D, Oki Y, Fayad L, et al. Phase I study of romidepsin in combination with ICE (ifosfamide, carboplatin, and etoposide) in patients with relapsed or refractory peripheral T-cell lymphoma. Blood. 2014;124:Abstract 1748.
[68] Velcade (bortezomib) [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc; 2015. [cited 2016 Apr 15]. Available from: http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf.
[69] Khan SB, Maududi T, Barton K, et al. Analysis of histone deacetylase inhibitor, depsipeptide (FR901228), effect on multiple myeloma. Br J Haematol. 2004;125:156–161.
[70] Catley L, Weisberg E, Kiziltepe T, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood. 2006;108:3441–3449.
[71] Pei XY, Dai Y, Grant S. Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor bortezomib and histone deacetylase inhibitors. Clin Cancer Res. 2004;10:3839–3852.
[72] Sutheesophon K, Kobayashi Y, Takatoku MA, et al. Histone deacetylase inhibitor depsipeptide (FK228) induces apoptosis in leukemic cells by facilitating mitochondrial translocation of bax, which is enhanced by the proteasome inhibitor bortezomib. Acta Haematol. 2006;115:78–90.
[73] Kikuchi J, Wada T, Shimizu R, et al. Histone deacetylases are critical targets of bortezomib-induced cytotoxicity in multiple myeloma. Blood. 2010;116: 406–417.
[74] Harrison SJ, Quach H, Link E, et al. A high rate of durable responses with romidepsin, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma. Blood. 2011;118:6274–6283.
[75] Liu FT, Agrawal SG, Gribben JG, et al. Bortezomib blocks bax degradation in malignant B cells during treatment with TRAIL. Blood. 2008;111:2797–2805.
[76] Faderl S, Rai K, Gribben J, et al. Phase II study of single-agent bortezomib for the treatment of patients with fludarabine-refractory B-cell chronic lymphocytic leukemia. Cancer. 2006;107:916–924.
[77] Liu FT, Agrawal SG, Movasaghi Z, et al. Dietary flavonoids inhibit the anticancer effects of the proteasome inhibitor bortezomib. Blood. 2008;112:3835–3846.
[78] Byrd JC, Shinn C, Ravi R, et al. Depsipeptide (FR901228): a novel therapeutic agent with selective, in vitro activity against human B-cell chronic lymphocytic leukemia cells. Blood. 1999;94:1401–1408.
[79] Aron JL, Parthun MR, Marcucci G, et al. Depsipeptide (FR901228) induces histone acetylation and inhibition of histone deacetylase in chronic lymphocytic leukemia cells concurrent with activation of caspase 8-mediated apoptosis and down-regulation of c-FLIP protein. Blood. 2003;102:652–658.
[80] Byrd JC, Marcucci G, Parthun MR, et al. A phase 1 and pharmacodynamic study of depsipeptide (FK228) in chronic lymphocytic leukemia and acute myeloid leukemia. Blood. 2005;105:959–967.
[81] Dai Y, Chen S, Kramer LB, et al. Interactions between bortezomib and romidepsin and belinostat in chronic lymphocytic leukemia cells. Clin Cancer Res. 2008;14:549–558.
[82] Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25:4293–4297.
[83] Cultrera JL, Rosenberg L, McConkey DJ, et al. The histone deacetylase inhibitor vorinostat induces apoptosis in T-cell lymphoma cell lines and synergizes with bortezomib. Blood. 2008;112:Abstract 1587.
[84] Holkova B, Kmieciak M, Bose P, et al. Phase 1 study of bortezomib and romidepsin in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, indolent B-cell lymphoma, peripheral T-cell lymphoma, or cutaneous T-cell lymphoma: updated results. Blood. 2014;124:Abstract 3050.
[85] McBride A, Klaus JO, Stockerl-Goldstein K. Carfilzomib: a second-generation proteasome

inhibitor for the treatment of multiple myeloma. Am J Health Syst Pharm. 2015;72:353–360.
[86] Akilov OE, Grant C, Frye R, et al. Low-dose electron beam radiation and romidepsin therapy for symptomatic cutaneous T-cell lymphoma lesions. Br J Dermatol. 2012;167:194–197.
[87] Jones SF, Infante JR, Spigel DR, et al. Phase 1 results from a study of romidepsin in combination with gemcitabine in patients with advanced solid tumors. Cancer Invest. 2012;30:481–486.
[88] Gemzar (gemcitabine for injection) [package insert]. Indianapolis, IN: Lilly USA; 2014. [cited 2016 Apr 15]. Available from: http://pi.lilly.com/us/gemzar.pdf.
[89] Sato N, Ohta T, Kitagawa H, et al. FR901228, a novel histone deacetylase inhibitor, induces cell cycle arrest and subsequent apoptosis in refractory human pancreatic cancer cells. Int J Oncol. 2004; 24:679–685.
[90] Rajgolikar G, Chan KK, Wang HC. Effects of a novel antitumor depsipeptide, FR901228, on humanbreast cancer cells. Breast Cancer Res Treat. 1998;51:29–38.
[91] Hirokawa Y, Arnold M, Nakajima H, et al. Signal therapy of breast cancers by the HDAC inhibitor FK228 that blocks the activation of PAK1 and abrogates the tamoxifen-resistance. Cancer Biol Ther. 2005;4:956–960.
[92] Vinodhkumar R, Song YS, Ravikumar V, et al. Depsipeptide a histone deacetlyase inhibitor down regulates levels of matrix metalloproteinases 2 and 9 mRNA and protein expressions in lung cancer cells (A549). Chem Biol Interact. 2007;165:220–229.
[93] Yu XD, Wang SY, Chen GA, et al. Apoptosis induced by depsipeptide FK228 coincides with inhibition of survival signaling in lung cancer cells. Cancer J. 2007;13:105–113.
[94] Vinodhkumar R, Song YS, Devaki T. Romidepsin (depsipeptide) induced cell cycle arrest, apoptosis and histone hyperacetylation in lung carcinoma cells (A549) are associated with increase in p21 and hypophosphorylated retinoblastoma proteins expression. Biomed Pharmacother. 2008;62:85–93.
[95] Khabele D, Son DS, Parl AK, et al. Drug-induced inactivation or gene silencing of class I histone deacetylases suppresses ovarian cancer cell growth: implications for therapy. Cancer Biol Ther. 2007;6:795–801.
[96] Lowell W, Wick MJ, Campos DR, et al. In vivo evaluation of depsipeptide (FK228) alone or in combination with gemcitabine in two human pancreas tumor xenograft models. Proc Amer Assoc Cancer Res. 2006;66:900–901.
[97] Gerber DE, Skelton R, Dong Y, et al. Phase I and pharmacodynamic study of the histone deacetylase (HDAC) inhibitor romidepsin plus erlotinib in previously treated advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2013;31:Abstract 8088.
[98] Janne PA, Johnson BE. Effect of epidermal growth factor receptor tyrosine kinase domain mutations on the outcome of patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors. Clin Cancer Res. 2006;12:4416s–4420s.
[99] Zhang W, Peyton M, Xie Y, et al. Histone deacetylase inhibitor romidepsin enhances anti-tumor effect of erlotinib in non-small cell lung cancer (NSCLC) cell lines. J Thorac Oncol. 2009;4:161–166.
[100] Burgess AJ, Pavey S, Warrener R, et al. Up-regulation of p21(WAF1/CIP1) by histone deacetylase inhibitors reduces their cytotoxicity. Mol Pharmacol. 2001;60:828–837.
[101] Cartee L, Wang Z, Decker RH, et al. The cyclin-dependent kinase inhibitor (CDKI) flavopiridol disrupts phorbol 12-myristate 13-acetate-induced differentiation and CDKI expression while enhancing apoptosis in human myeloid leukemia cells. Cancer Res. 2001;61:2583–2591.
[102] Schrump DS, Matthews W, Chen GA, et al. Flavopiridol mediates cell cycle arrest and apoptosis in esophageal cancer cells. Clin Cancer Res. 1998;4:2885–2890.
[103] Nguyen DM, Schrump WD, Tsai WS, et al. Enhancement of depsipeptide-mediated apoptosis of lung or esophageal cancer cells by flavopiridol: activation of the mitochondria-dependent death-signaling pathway. J Thorac Cardiovasc Surg. 2003;125:1132–1142.
[104] Abraxane (paclitaxel protein-bound particles for injectable suspension) [package insert]. Summit, NJ: Celgene Corporation; 2015. [cited 2016 Apr 15]. Available from: http://www.abraxane.com/wp-content/uploads/Abraxane_Prescribing_Information.pdf.
[105] Robertson FM, Chu K, Boley KM, et al. The class I HDAC inhibitor romidepsin targets inflammatory breast cancer tumor emboli and synergizes with paclitaxel to inhibit metastasis. J Exp Ther Oncol. 2013;10:219–233.
[106] Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol. 2010;28:1145–1153.
[107] Wilson AJ, Lalani AS, Wass E, et al. Romidepsin (FK228) combined with cisplatin stimulates DNA damage-induced cell death in ovarian cancer. Gynecol Oncol. 2012;127:579–586.