Use of class I histone deacetylase inhibitor romidepsin in combination regimens

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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.

Introduction

In eukaryotic cell nuclei, genomic DNA is assembled onto histone proteins, which aid in packaging into nucleosomes, the repeating units of chromatin. Histones undergo a wide variety of modifications that have significant effects on gene expression, including acetylation, methylation, phosphorylation, and ubiquitination. 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. 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. Equilibrium between HAT and HDAC activity is needed for normal cell growth and differentiation, and perturbation of that equilibrium due to aberrant expression, function, and/or alteration of HDAC genes has been associated with various cancers.

Human HDACs are divided into 4 classes (I–IV). Classes I, II, and IV HDACs are zinc-dependent and the targets of HDAC inhibitors in clinical development. Class III HDACs (sirtuins 1–7) are NAD⁺-dependent and unaffected by current HDAC inhibitors. Inhibition of HDACs prevents removal of acetyl groups from histone and nonhistone proteins, which allows DNA to remain transcriptionally active and maintains protein function. 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.

Several HDAC inhibitors with varying structural class, specificity, and potency are under investigation as anticancer agents. 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 therapy and the treatment of peripheral TCL (PTCL) in patients who have received at least 1 prior therapy. 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
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/biological 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 withAITL; including this patient, 4 of 5 patients withAITL 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, including 11/39 (28%).[29,30] A clinically meaningful reduction in pruritus (≥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 ≥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 \(\geq 3\) 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 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 \(\geq 3\) AE, the most common (\(\geq 10\%\)) of which were neutropenia (48%), thrombocytopenia (38%), anemia (33%), and electrolyte abnormalities (43%).\[45\] A separate phase I/II 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.
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/m² + alisertib 20 mg twice daily (BID), romidepsin 10 mg/m² + alisertib 20 mg BID, romidepsin 10 mg/m² + alisertib 40 mg BID, romidepsin 12 mg/m² + alisertib 40 mg BID, and romidepsin 14 mg/m² + 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] |
| Bortezomib (proteasome inhibitor) | Ph 1/2 in previously untreated PTCL (N = 37; NCT01280526) [64] | - 54% ORR (7/13) including 67% (4/6) of those with TCL |
| Decitabine (hypomethylator) | Ph 1b/2 in previously untreated TCL (N = 25; NCT00431990) [74] | - Of 35 evaluable pts, 69% ORR including 51% CR [64] |
| ICE (chemotherapy) | Of 18 evaluable pts, 1 PR (CLL) and 9 SD (6 CLL/SLL, 1 TCL, 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) |
| Bortezomib (proteasome inhibitor) | Ph 1/2a + dexamethasone in R/R MM (N = 25; NCT007099276) |
| CC-486 (oral azacitidine; hypomethylator) | Ph 1/2 in R/R lymphoid malignancies (N = 60; NCT01998035) |
| CHOEP (anthracycline-based chemotherapy) | Ph 1/2 prior to SCT in young pts (18–65 y) with untreated nodal PTCLs (N = 110; NCT02223208) |
| Gemcitabine (nucleoside analog) | Ph 1a in R/R TCCL (N = 6; NCT01610020a) |
| GemOx + dexamethasone (gemcitabine-containing regimen) | Of 18 evaluable pts, 1 PR (CLL) and 9 SD (6 CLL/SLL, 1 TCL, 2 indolent BCL) [84] |
| Carfilzomib (proteasome inhibitor) | Of 25 evaluable pts, 72% ORR (all CR) [67] |

This study noted twice in table, in both the lenalidomide and carfilzomib sections.

This study is listed as complete; however, no data have been reported to date.

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 B-cell lymphoma (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 pulm-
ony and pleural malignancies (± celecoxib; N = 34; 
NCT00037817), were initiated. Both studies are com-
plete, but neither has reported safety or efficacy data. 
Newer studies have focused on CC-486 (oral azaciti-
dine). Hypomethylating effects are cell-cycle depend-
ent [61]; several cycles of DNA replication are required 
for DNA hypomethylation,[62] and extensive demethy-
lation 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 liposar-
coma, 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 refrac-
tory TCL suggests that combination with chemother-
apy has the potential to prolong remissions.

**Anthracline-based therapies**

The majority of patients with PTCL receive anthracy-
cline-based therapies (e.g. CHOP [cyclophosphami-
de + 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 Iб) and dose-
expansion (phase II) study in patients with previously 
untreated PTCL (N = 37).[64] In the phase Iб 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/m² on days 1 and 8. Reported DLTs included 
syncope (without sequelae), neutropenia, hyponatre-
mia/hyponophatemia, pulmonary edema, and vomit-
ing. Romidepsin 12 mg/m² was chosen for the phase II 
portion (n = 19). Grade ≥ 3 hematologic toxicity 
occurring in the majority of patients (N = 37), with most 
common nonhematologic events categorized as gastrointest-
inal, 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 I б/
II results led to initiation of a phase III study of CHOP 
versus 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 ther-
apy 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/m² 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 thrombocto-
penia 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 sal-
vage 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 gemcitab-
ine 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 romidep-
sin + 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 protea-
some inhibitors and HDAC inhibitors has been
demonstrated in MM cells. In a phase I/II study in patients with relapsed/refractory MM, bortezomib (1.3 mg/m² 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/m² on days 1, 8, and 15) in 28-day cycles (N = 25). Reported DLTs included thrombocytopenia, febrile neutropenia, intracerebral hemorrhage, and bowel obstruction. The MTD of romidepsin was 10 mg/m². 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). 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. In a phase II study of bortezomib 1-1.5 mg/m² on days 1, 4, 8, and 11 of 21-day cycles in CLL (N = 22), no objective responses were reported. It was later shown that dietary flavonoids abundant in plasma inhibit bortezomib in patients with CLL. Romidepsin showed selective cytotoxicity toward CLL cells vs. normal peripheral blood mononuclear cells as well as histone H3 and H4 acetylation, HDAC enzyme inhibition, and apoptosis in cultured CLL cells. In a phase I study of romidepsin 13 mg/m² 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. Bortezomib + romidepsin (or belinostat) synergistically induced cell death in primary and cultured CLL cells. Bortezomib is also a suggested salvage regimen for patients with PTCL who are not candidates for high-dose therapy. A phase II study demonstrated activity in relapsed/refractory CTCL. Synergy was also shown for the HDAC inhibitor vorinostat + bortezomib in TCL cell lines. In a phase I study, a standard 3 + 3 dose-escalation scheme was used to combine romidepsin (8 or 10 mg/m² on days 1, 8, and 15) + bortezomib (1.3 or 1.6 mg/m² 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). Three DLTs occurred (fatigue, chills, and vomiting; all grade 3), and the MTD was romidepsin 10 mg/m² + bortezomib 1.3 mg/m². 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).

Carfilzomib is a new-generation proteasome inhibitor associated with less peripheral neuropathy than bortezomib. 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. In 5 patients with advanced CTCL who received low-dose electron beam radiation and romidepsin, 4 demonstrated rapid and durable responses. 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.

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