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Role of allogeneic stem cell transplantation in mantle cell lymphoma

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Abstract

Despite a wide spectrum of treatment options, mantle cell lymphoma (MCL) remains a challenging hematologic malignancy to manage. Advances in front-line therapy, including the monoclonal antibody rituximab and increasing use of cytarabine, have improved remission rates. Autologous hematopoietic cell transplantation (HCT) can effectively consolidate remission of MCL, leading to encouraging survival beyond 5 yr. However, nearly all patients with MCL will relapse and require salvage therapy. Novel agents such as ibrutinib, bortezomib, and lenalidomide have dramatically expanded the options for treating relapsed MCL. In this review, we summarize the clinical evidence supporting the use of allogeneic donor HCT in MCL and make recommendations on indications for its use. Data suggest that allogeneic donor HCT is the only curative therapy for patients with poor prognosis or aggressive MCL. Patient selection, timing, and optimal use remain a matter of scientific debate and given the rapidly changing therapeutic landscape of MCL, the outcomes of allogeneic HCT should be interpreted in the context of novel therapeutics.

Keywords
mantle cell lymphoma; allogeneic donor; hematopoietic cell transplantation; review

Introduction

Risk stratification in mantle cell lymphoma

Mantle cell lymphoma (MCL) comprises <10% of cases of non-Hodgkin’s lymphoma (NHL) and is generally considered incurable with standard therapies. Patients often present with extranodal disease including bone marrow and gastrointestinal involvement, and peripheral blood lymphocytosis is also frequently encountered. Risk stratification in MCL combines clinical, laboratory, radiologic, and molecular markers (Table 1). The MCL International Prognostic Index (MIPI) combines age, performance status, lactate

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dehydrogenase, and leukocyte count at diagnosis to predict overall survival (OS) by segregating patients into three prognostic categories of low, intermediate, and high-risk disease. In their initial report, Hoster et al (1) reported that low MIPI was associated with a median OS which was not reached during the 32-month follow-up period. Patients with intermediate-risk MIPI had a median OS of 51 months, and patients with high-risk MIPI had a median OS of only 29 months. Recently, Hoster et al (2) reported outcomes from the European MCL Network prospective trial that indicated that MIPI continues to be a robust clinical tool for risk stratification in patients treated with modern cytarabine-containing regimens followed by autologous HCT or rituximab maintenance for patients who are not transplant candidates. The Ki67 proliferative index is also prognostic for outcome, although the specific cutoff value that divides high- vs low-risk patients has not been determined (1–4). Genetic risk-stratification is also advancing rapidly. The hallmark of MCL is the chromosomal translocation t(11;14) resulting in aberrant expression of cyclin D1. In addition, secondary events increase the oncogenetic potential of cyclin D1 including an increased number of chromosomal abnormalities (i.e., a complex karyotype) and mutations in specific genes such as NOTCH1, SOX11, and tumor suppression gene TP53 (5–9). Despite increasing knowledge regarding the underlying genetics of MCL, treatment decisions are not often influenced by underlying genetics or Ki67. Finally, depth of response to induction therapy prior to autologous hematopoietic cell transplant (HCT) can be predictive of survival as shown in recent preliminary studies (10, 11). Patients with a positive positron emission tomography/computed tomography (PET/CT) prior to autologous HCT have higher relapse rates compared to those who achieve a negative PET/CT.

**Treatment options in MCL**

There is no current standard front-line therapy for patients with MCL, although several effective regimens are utilized. Combination chemotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by autologous HCT yields a median progression-free survival (PFS) of 39 months compared to 17 months for patients managed without autologous HCT as consolidation (12). More recently, cytarabine-containing induction or mobilization regimens have resulted in prolonged PFS. Treatment with cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (HyperCVAD) followed by autologous HCT led to 5-yr progression-free survival (PFS) of 43%. In a single-institution study, addition of rituximab to HyperCVAD remarkably improved 5-yr PFS to 73% (13, 14). The Alliance for Clinical Trials in Oncology (Alliance; formerly Cancer and Leukemia Group B) cooperative group conducted a study testing augmented R-CHOP with methotrexate (CALGB 59909) followed by chemo-mobilization with cytarabine, etopside, and rituximab prior to autologous HCT. In the CALGB 50403 trial, post-transplant bortezomib was added (15, 16). PFS at 5 yr in the CALGB 59909 trial was 56%, and PFS at 3 yr in the CALGB 50403 trial was 67%, suggesting a role for post-transplant bortezomib. Another effective induction strategy alternates R-CHOP with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) prior to autologous HCT and yields remarkable median event-free survival of 83 months (17). Increasingly, bendamustine plus rituximab (B-R) has been used as a promising induction for older patients (18). Maintenance rituximab can be considered for transplant ineligible patients treated initially with R-CHOP or HyperCVAD.
In addition, the Wisconsin Oncology Group demonstrated a 3-yr PFS of 63% and overall survival (OS) of 86% in a cohort of patients with median age of 61 yr who received bortezomib combined with a modified R-hyperCVAD regimen (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) followed by maintenance rituximab (20).

While these induction strategies and autologous HCT may lead to prolonged remission, nearly all patients will ultimately relapse and require additional therapy. Until recently, outcomes for patients who relapse after autologous HCT have been poor. The median OS for relapsed patients reported in a recent European Group for Blood and Marrow Transplantation (EBMT) report was only 19 months (21). Allogeneic HCT represents a potential treatment option for patients with MCL, including those who relapse after autologous HCT. Allogeneic transplant procedures are advancing through use of reduced-intensity conditioning (RIC) regimens and alternative donor graft sources. These strategies allow for broader application of the immune-mediated anti-lymphoma effect. Allogeneic HCT remains the sole curative therapeutic option for MCL, although patient selection, timing, and optimal use are areas of active research. We will review the data on allogeneic transplantation in MCL including the including prognostic systems and therapeutic limitations.

**Allogeneic transplant for relapsed/refractory MCL**

**Historical use of allogeneic transplant in MCL**

Initial reports of successful outcomes for allogeneic transplant in MCL appeared in the 1990’s incorporated myeloablative conditioning regimens. One early report on the use of cyclophosphamide/thiotepa conditioning regimen followed by an HLA-identical sibling transplant demonstrated that complete remission (CR) and sustained molecular remission could be achieved following autologous HCT relapse (22). Another case report of a patient with chemorefractory MCL treated with total body irradiation (TBI), etoposide, and cyclophosphamide and sibling HCT demonstrated persistent disease in the blood by morphology until day+20 post-transplant followed by subsequent resolution and CR at 1-yr follow-up with limited cutaneous chronic graft-versus-host disease (GVHD) (23). These reports illustrate the potency of the graft-versus-lymphoma effect in MCL. A larger series of 16 patients reported by the MD Anderson group (14 received a myeloablative regimen) showed 3-yr PFS of 55%; chemo-sensitive disease prior to transplant significantly improved long-term survival. Out of the 16 patients, there were 6 non-relapse-related deaths, including 3 from GVHD, 1 from infection, 1 from multiorgan failure, and 1 from graft failure (24).

**Conditioning regimen intensity and outcomes using RIC**

Allogeneic transplant for MCL is most commonly utilized for relapsed and refractory disease. Myeloablative transplant is often not an option for many patients given the median age of MCL, extensive prior therapy (often preceding autograft), and co-morbidities. RIC regimens were developed to facilitate donor cell engraftment; elicit a subsequent immune-mediated, anti-lymphoma effect; and spare patients the undesired effects of prolonged myelosuppression and organ toxicity.
Several retrospective analyses have indirectly compared RIC with myeloablative regimens for multiple non-Hodgkin lymphoma subtypes, including MCL (25–27). One report from the City of Hope compared outcomes after myeloablative (10 patients) and RIC regimens (5 patients). The 2-yr relapse rate after RIC (60%) was higher compared to the myeloablative cohort (20%); however, TRM was lower in the RIC cohort leading to the same 2-yr OS (53% RIC; 52% myeloablative) (27). A University of Minnesota series evaluated 115 consecutive patients with various NHL subtypes and compared outcomes by conditioning (26). The 4-yr OS for myeloablative conditioning was 46% compared to 49% for RIC, with no differences in OS or PFS and no impact of GVHD or patient or disease characteristics on survival. A subsequent report on 28 allo-HCT recipients with MCL (half had RIC and 30% received umbilical cord blood) showed encouraging 5-yr OS of 53% (11). The MD Anderson group reported a RIC HCT series of 18 patients with relapsed or progressive MCL. All except 2 patients were in complete or partial remission. Outcomes were excellent with a 3-yr OS of 85.5%, with only 3 deaths in the cohort secondary to progression, to GVHD, and 1 death unrelated to therapy (28). A larger, multicenter study of the EBMT included 22 patients with both chemorefractory and chemosensitive disease. RIC HCT resulted in a 1-yr probability of disease progression of 48% and PFS of 31% (29). Patients with chemorefractory disease had increased transplant-related mortality and incidence of progression, although an analysis of the MCL subset based on response to therapy was not reported. Le Gouill et al. (30) reported outcomes for 70 patients with RIC regimens for relapsed MCL. Two-year treatment-related mortality was 22%, and the 2-yr event-free and OS were 50% and 53%, respectively. In a recent Center for International Bone and Marrow Transplantation Research (CIBMTR) retrospective analysis, Fenske et al. (31) included 88 patients with chemosensitive relapsed disease. Patients with a prior autologous HCT were excluded. The 5-yr PFS for patients undergoing RIC allogeneic transplant was 24%, and the 5-yr relapse rate was 51%. The non-relapse mortality rate was 17% at 1 yr, yielding a 5-yr OS of 31%. Outcomes for patients undergoing a RIC allogeneic transplant are presented in Table 2.

**Impact of initial remission duration and disease status at transplant**

Disease status at transplant appears to be of particular importance, although prolonged remission is still possible even among patients with refractory disease. Hamadani et al. (32) identified 202 patients with chemorefractory MCL reported to CIBMTR; 128 were RIC HCT. The estimated 3-yr PFS and OS were 25% and 30%, respectively, and outcomes were not different after myeloablative or RIC conditioning. Remarkably, non-relapse mortality remained high at 43% regardless of conditioning intensity. Cumulative incidence of relapse was 32% at 3 yr. In a single-center study of 46 refractory NHL patients (including 11 with MCL), the 5-yr OS and PFS was 18% and non-relapse mortality was very high at 55% (33). The high incidence of non-relapse death suggests that patients with active disease have significantly increased risk of transplant-related complications aside from their risk of disease relapse.

The British Society for Blood and Marrow Transplantation (BSBMT) reported outcomes for 70 patients with MCL undergoing an RIC allogeneic transplant, including 11 patients with refractory disease at the time of transplant. While the OS at 3 yr was 60% for patients with a
complete remission (CR) at the time of transplant, only 38% of patients with refractory disease were alive. The 3-yr PFS for patients with refractory disease was 0%, compared to 31% for patients with CR (34).

Additionally, duration of remission postautologous HCT may predict outcomes for patients undergoing subsequent allogeneic transplant. In a review from the EBMT of 360 patients with MCL that relapsed after an autologous HCT, 80 patients subsequently underwent an allograft (21). Patients who experienced a relapse >12 months after autologous HCT had improved OS (HR 0.32, P = 0.001) compared to patients who experienced relapse prior to that time period. Among patients who had relapsed more than 1 yr after autologous HCT and who had chemosensitive disease at relapse, the 5-yr OS was 60%.

**Prospective studies in relapsed MCL**

Prospective studies in MCL are scarce and limited by small sample size. Khouri and colleagues reported a novel conditioning regimen that combined high-dose rituximab peritransplant (4 weekly infusions) with an RIC fludarabine/cyclophosphamide backbone. At a median follow-up of 26 months, 18 MCL patients experienced outstanding long-term PFS and OS with a 3-yr estimate of 82% and 85%, respectively (28). In a prospective study at the Fred Hutchison Cancer Research Center, 33 MCL patients were transplanted after receiving a RIC regimen of fludarabine and 2 Gy of TBI; the encouraging 2-yr PFS was 60% and the relapse rate was 16% (35). More than 4 prior regimens increased the risk of relapse. Two-year non-relapse mortality was 24%, and 2-yr OS was 64%. Another prospective series on 12 patients treated with allogeneic transplant using the RIC regimen of fludarabine/treosulfan ± rituximab reported PFS and OS medians of 2.9 yr, although young patients experienced improved disease control with decreased toxicity (36). The Grupo Español de Linfomas y Trasplante de Médula Osea (GELTAMO) study of 21 patients conditioned with the RIC regimen of fludarabine and melphalan demonstrated an encouraging 5-yr PFS and OS of 80%, with a non-relapse mortality of 19% (37).

Radio-immunotherapy has also been incorporated into allogeneic transplant trials for NHL. Gopal et al (38). reported a prospective trial of 40 patients with B-cell NHL (including 8 with MCL) who received an RIC regimen of 90Y-ibritumomab tiuxetan followed by fludarabine and TBI. Four of the 8 patients experienced a remission (CR or partial remission [PR]), and the estimated 6-month PFS for 8 patients with MCL was 50%. There were no long-term remissions in the MCL cohort, although outcomes for specific patients were not reported. In another series that incorporated 90Y-ibritumomab tiuxetan as part of an RIC regimen, the 2-yr OS was 37% for the 8 patients with MCL (39, 40).

On the basis of these reports, it appears that prospectively selected patients with MCL treated with an RIC fludarabine-based preparative regimen may enjoy prolonged survival. However, a cautious interpretation is needed as we apply these outcomes to all patients because the eligibility requirements related to health and disease status during enrollment on a prospective study is highly selective. At this time, it appears that patient selection and disease status at transplant are likely more important than any particular conditioning regimen. To determine the optimal preparative therapy prior to allograft, a larger, prospective study is required.
Allogeneic transplant as consolidation for patients in first remission

Allogeneic transplant has also been investigated as part of up-front therapy in patients in first remission. In a recent analysis by the CIBMTR, patients with MCL undergoing RIC allogeneic transplant were compared to those undergoing autologous transplant (31). Fifty patients who underwent RIC allogeneic transplant in first remission (PR or CR) between 1996 and 2007 were compared to 249 patients who underwent autologous transplant in first remission. Patients receiving myeloablative allogeneic HCT were excluded. The 5-yr incidence of relapse/progression was significantly lower after allogeneic (15%) compared to autologous HCT (32%, \( P = 0.009 \)), but at the expense of a significant increase in non-relapse mortality at 1-yr in the allogeneic cohort (25% vs. 3%, \( P < 0.001 \)). As a result, the 5-yr PFS and OS were similar in the two groups (OS: 61% vs. 62%, respectively). Evens and colleagues conducted a phase II study in which patients completed intensive cytarabine-containing induction therapy with planned allogeneic sibling HCT for patients younger than 55 yr of age with an available sibling donor. Patients \( \geq 5 \) yr (including those without a matched related donor) received autologous transplant in first remission, while the remaining patients completed maintenance immunotherapy. Only four of 25 enrolled patients completed allogeneic transplant; 3 died from progressive disease (\( n = 2 \)) or GVHD complications (\( n = 1 \)), while one patient had long-term relapse-free survival (41). The East German Study Group Haematology/Oncology (OSHO) reported outcomes from parallel trials utilizing allogeneic transplant in the relapsed versus front-line setting. Notably, the median PFS and OS were not significantly different between the two groups, and the overall 5-yr PFS was 67% when considering all patients (36). Cruz et al (37), included a subset of patients in first remission in their study of 21 patients (3 of whom had prior autologous transplant), and while the results of the subgroup in first remission were not reported separately, the cumulative incidence of non-relapse mortality at 3 yr was 19.5%, with only one patient experiencing a relapse during follow-up. As a result, the 5-yr PFS and OS rates were 80%. In a report from the University of Minnesota, six patients underwent allogeneic transplant in first complete or partial remission, resulting in a 5-yr disease-free survival of 40% versus 42% for patients with relapsed disease (42).

Although a direct prospective comparison has not been completed, the aggregate data suggest that allogeneic transplant yields similar efficacy in first or subsequent remission in MCL. Given the higher treatment-related mortality associated with allogeneic transplant compared to autologous transplant, there is no indication at present to recommend allogeneic transplant for patients in first PR or CR.

Management of relapse after allogeneic transplant

Relapse after allogeneic HCT can be treated with additional therapy and strategies to elicit graft-versus-lymphoma effects. A University of Minnesota series of 72 patients with lymphoma who relapsed after allogeneic transplant (including 7 patients with MCL) resulted in a median postrelapse survival of 25 months (43) The median 3-yr OS for the MCL subset was remarkable at 43%. Strategies that have had anecdotal success include immunologic approaches (e.g., CD20-targeted monoclonal antibodies), immunosuppression withdrawal, donor lymphocyte infusion, and second allogeneic HCT. Standard salvage regimens are
options for therapy, and interestingly, one case report identified a patient who received donor lymphocyte infusions, interferon, rituximab, and bortezomib at various times for post-transplant relapse and remained alive 10-yr post-allogeneic transplant despite multiple episodes of relapse (44). This case illustrates the feasibility of subsequent therapies and that prolonged remissions are possible but uncommon. Importantly, patients are often best served through consideration of a clinical trial using an investigational agent (Table 3).

**Conclusions**

Although the available therapies for MCL improve survival, the prognosis of patients with relapsed disease remains poor, with OS <2 yr (21). Recent advances using bortezomib, lenalidomide, and ibrutinib extend the treatment options and improve remission rates and disease-free periods (Table 3) (45–47). However, to date, none has been shown to be curative in MCL. Likewise, the majority of patients relapse following autologous HCT. In contrast, allogeneic HCT affords the possibility of a cure in a subset of patients. However, outcomes vary based on conditioning regimen intensity, disease-free interval after autologous HCT, duration of remission, and depth of remission at time of allogeneic HCT. Furthermore, non-relapse mortality is significant.

We recommend that patients who relapse after an autologous HCT and demonstrate chemosensitivity to a salvage regimen should be strongly considered for an RIC allogeneic transplant. Several recent publications reported favorable transplant outcomes using an alternative donor source; therefore, donor availability should not be a barrier to allograft. We propose an algorithm for timing and consideration of allogeneic transplant in MCL in Fig. 1. Outcomes of allogeneic HCT for MCL are promising and proper patient selection leads to cure rates ranging from 35% to 65%. Allogeneic HCT for MCL in first remission should be used sparingly and only for healthy younger patients unable to mobilize stem cells for an autograft or who are, albeit exceedingly rare, primary chemoresistant. Both RIC and myeloablative conditioning can be considered, with the choice guided by patient age, disease, and co-morbidities. All other patients benefit from a consolidation strategy with autologous HCT in first remission. Younger healthy patients with short duration of response after autologous HCT or those with very high-risk features (e.g., high MIPI, p53 mutation) should be considered for allogeneic HCT at the time of first relapse. Patients with multiple relapses, treated with >4 lines of chemotherapy or refractory to MCL have not only a high relapse risk, but also increased rates of treatment-related mortality. Nevertheless, a proportion of these patients (20–25%) can survive disease-free long term. The increasing use of RIC regimens offers elderly patients and those with comorbidities the possibility of prolonged PFS; however, allogeneic HCT needs to considered, while the disease is still chemo-sensitive. Older patients with chemorefractory disease may benefit from new-targeted therapies or enrollment in a clinical trial.

**Future directions in therapy for MCL**

Future research in MCL must include genetic and molecular markers to refine disease-stratification, particularly early identification of patients who are expected to experience only a short-term benefit from standard chemotherapy. Evaluation for p53 mutation and
SOX11 could provide guidance in clinical practice. Clinical trials for relapsed MCL could improve outcomes following allogeneic HCT by post-transplant consolidation with the CD20-targeting agents, ibrutinib or lenalidomide, as well as by incorporating innovations in supportive care and advances in management of GVHD.

References


Figure 1.
Suggested approach for integration of allogeneic transplant in management of relapsed/refractory mantle cell lymphoma.
Table 1
Clinically useful prognostic tools for newly diagnosed mantle cell lymphoma

<table>
<thead>
<tr>
<th>White Blood Cell Count</th>
<th>MCL International Prognostic Index (MIPI)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
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<tr>
<td>Lactate Dehydrogenase</td>
<td></td>
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<tr>
<td>ECOG Performance Status</td>
<td></td>
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<tr>
<td>Ki67 Proliferative Index</td>
<td></td>
</tr>
<tr>
<td>Pretreatment Cytogenetics</td>
<td>(Complex karyotype and del17p)</td>
</tr>
<tr>
<td>Series</td>
<td>N</td>
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<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>Khouri et al. (28)</td>
<td>18</td>
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<tr>
<td>Robinson et al. (29)</td>
<td>22</td>
</tr>
<tr>
<td>Le Gouill et al. (30)</td>
<td>70</td>
</tr>
<tr>
<td>Maris et al. (35)</td>
<td>33</td>
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<tr>
<td>Gayoso Cruz et al. (37)</td>
<td>21</td>
</tr>
<tr>
<td>Maris et al. (35)</td>
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</tr>
<tr>
<td>Gopal et al. (36)</td>
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<tr>
<td>Bethge et al. (40)</td>
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<tr>
<td>Fenske et al. (31)</td>
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<tr>
<td>Hamadani et al. (32)</td>
<td>128</td>
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<tr>
<td>Cook et al. (34)</td>
<td>70</td>
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<tr>
<td>Magnusson et al. (11)</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 2
Outcomes patients undergoing reduced-intensity conditioning allogeneic transplants for mantle cell lymphoma.
### Table 3
Selected currently approved and investigational therapies for relapsed mantle cell lymphoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Food and Drug Administration Status/Clinical Trial Phase</th>
</tr>
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<tbody>
<tr>
<td>Ibrutinib</td>
<td>Bruton’s Tyrosine Kinase Inhibitor</td>
<td>Approved</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome Inhibitor</td>
<td>Approved</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Immunomodulator</td>
<td>Approved for patients previously treated with bortezomib</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>PI3-kinase inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Everolimus/Temsirolimus</td>
<td>mTOR inhibitors</td>
<td>Phase 2 and 3</td>
</tr>
<tr>
<td>Alisertib</td>
<td>Aurora A Kinase Inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>HDAC inhibitor</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ABT-199</td>
<td>BCL-2 inhibitor</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

mTOR, mammalian target of rapamycin; HDAC, histone deacetylase.