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A Phase I/II Trial of Panobinostat in Combination With Lenalidomide in Patients With Relapsed or Refractory Hodgkin Lymphoma

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Abstract

On the basis of previous studies showing single-agent efficacy with lenalidomide and panobinostat in patients with relapsed or refractory Hodgkin lymphoma (HL), we conducted a phase I/II study to evaluate the safety and efficacy of the combination in this patient population. The recommended phase II dose was 25 mg lenalidomide on days 1 to 21 with 15 mg panobinostat 3 times per week, and an overall response rate of 16.7% in patients was observed, with a durable response in 1 patient with lymphocyte-predominant HL.

Background—Lenalidomide and panobinostat have shown single-agent efficacy of 14% to 50% and 27% to 58%, respectively, in Hodgkin lymphoma (HL). This phase I/II study was conducted to determine the maximum tolerated dose (MTD), safety, and efficacy of lenalidomide combined with panobinostat in relapsed/refractory HL.

Patients and Methods—In the phase I trial, previously treated patients with classical or lymphocyte-predominant HL received escalating doses of lenalidomide on days 1 to 21 and panobinostat 3 times a week (TIW) every 28 days. Dose-limiting toxicity (DLT) was defined during cycle 1. When the MTD was determined, a phase II study was conducted to determine overall response (OR).

Results—Twenty-four patients enrolled; 11 in the phase I and 13 in phase II portions. No DLTs were observed but 2 patients who received 25 mg lenalidomide and 20 mg panobinostat experienced neutropenia and thrombocytopenia > 14 days in cycle 2, leading to selection of 25 mg lenalidomide on days 1 to 21 and 15 mg pan-obinostat TIW for the phase II dose. In all 24 patients, Grade 3 to 4 toxicities consisted of neutropenia (58%), throm-bocytopenia (42%),

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This trial is registered at clinicaltrials.gov: NCT01460940.

Disclosure

Novartis Pharmaceuticals provided panobinostat and Celgene Corporation provided lenalidomide for this trial. K.A. Blum, B. Christian, N.L. Bartlett, N.D. Wagner-Johnston, and T.A. Fehniger receive clinical trials support from Celgene and K.A. Blum receives clinical trials support from Novartis Pharmaceuticals. The remaining authors declare no competing financial interests.

lymphopenia (25%), and febrile neutropenia (25%). OR was 16.7% (2 complete response [CR] and 2 partial response). One patient with CR had lymphocyte-predominant HL and received 22 cycles. Median progression-free survival and overall survival were 3.8 and 16.4 months, respectively.

Conclusion—Although the combination of panobinostat and lenalidomide appears safe in patients with relapsed/refractory HL, the limited efficacy and significant rates of neutropenia and febrile neutropenia observed do not support further evaluation of this combination in HL.

Keywords

Clinical trial; Hodgkin's lymphoma; Relapsed/refractory; Lenalidomide; Panobinostat

Introduction

Despite the efficacy of brentuximab vedotin and the checkpoint inhibitors pembrolizumab and nivolumab^{1–3} in patients with relapsed or refractory classical Hodgkin lymphoma (HL), the duration of response is still unclear and novel therapies are still needed for this population. Two agents that have shown single-agent activity in this setting are the immunomodulatory agent, lenalidomide, and the histone deacetylase inhibitor, panobinostat.

Lenalidomide produces in vitro dose-dependent cell cycle arrest⁴ and inhibits the AKR mouse thymoma kinase signaling pathway⁵ in lymphoproliferative disorders. Additionally it enhances natural killer cell type immunity and T-cell cytotoxicity.⁶ In a multicenter trial in patients with relapsed classical HL (cHL) of lenalidomide (25 mg on days 1–21 of a 28-day cycle), an overall response rate (ORR) of 19% for evaluable patients and a cytostatic response rate (complete response [CR], partial response [PR], or stable disease [SD] 6 months) of 31.6% for all patients were reported.⁷ In this trial, the median time to treatment failure for patients with SD or better was 15 months, with some responders continuing therapy for > 3 years. Another smaller phase II trial with lenalidomide monotherapy also in patients with refractory or multiple relapsed HL showed an ORR of 50%.⁸

Similarly, in HL cell lines, panobinostat shows an anti-proliferative effect through activation of the caspase pathway and inhibition of signal transducer and activator of transcription (STAT) 5 and 6 phosphorylation.⁹ In a phase II multicenter trial with panobinostat (40 mg 3 times per week) in 129 patients with relapsed/refractory HL after a previous autologous stem cell transplantation, the ORR was 27%, the disease control rate (CR, PR, and SD) was 82%, and the median duration of response was 6.9 months.¹⁰ As seen with lenalidomide, several of these patients had prolonged responses, and continued therapy up to 15 months.

On the basis of this single-agent activity of lenalidomide as well as panobinostat separately in patients with relapsed or refractory cHL, we conducted a phase I/II trial to determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and ORR with combined lenalidomide and panobinostat in patients with relapsed/ refractory HL. Preclinical evaluation of these 2 agents in combination with dexamethasone in multiple myeloma cell lines showed synergistic cell-killing compared with single-agent therapy assessed using the Chao-Talalay statistical model and subsequent measurement of ex vivo apoptosis. In the

same article it was reported that in a plasmacytoma murine model, this combination again compared with single-agent panobinostat led to a statistically significant survival benefit (88 days vs. 70 days respectively; $P < .001$) as well as a statistically significant decrease in tumor size (P values ranging between .01 and .04) correlating with reduced Ki-67 expression and the apoptotic markers caspase-3 and poly ADP ribose polymerase.¹¹ Furthermore, in a phase II trial in patients with relapsed/refractory multiple myeloma an ORR of 45% was observed with combination lenalidomide, panobinostat, and dexamethasone, with responses observed in lenalidomide-refractory patients.¹²

Patients and Methods

Patient Eligibility

This open-label, multicenter phase I/II trial was conducted at The Ohio State University, James Comprehensive Cancer and Washington University, Siteman Cancer Center from February 2012 through January 2015 to determine the safety, tolerability, and efficacy of combined panobinostat and lenalidomide in patients with relapsed and refractory classical and lymphocyte-predominant (LP) HL. The protocol was approved by The Ohio State and Washington University institutional review boards and conducted in accordance with the Declaration of Helsinki. The trial is registered at www.clinicaltrials.gov as NCT01460940 and all patients provided written informed consent.

Patients 18 years of age and older with classical or LP HL according to World Health Organization criteria¹³ previously treated with (at least) 1 previous cytotoxic chemotherapy were eligible. Previous autologous or allogeneic stem cell transplantation was permitted. Patients were permitted to have received previous panobinostat or lenalidomide. Additional eligibility criteria included measurable disease > 1 cm, left ventricular ejection fraction $\geq 45\%$, Eastern Cooperative Oncology Group performance status of 0 to 2, absolute neutrophil count $\geq 1200/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, aspartate transaminase and alanine transaminase ≤ 2.5 times the upper limit of normal (ULN), bilirubin ≤ 1.5 times the ULN, and creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault calculation. Patients with any of the following conditions: pregnancy or nursing, HIV or hepatitis B or C, central nervous system lymphoma, preexisting gastrointestinal disease that could impair drug absorption, history of cardiac arrhythmia, or QTc on screening electrocardiogram > 450 ms were not eligible.

Treatment

Phase I Trial—Refer to Table 1 for a depiction of the treatment schedule. The treatment cycle was 28 days and patients could continue to receive therapy until disease progression. Panobinostat was administered orally on days 1, 3, and 5 weekly at escalating doses as shown in Table 1. Lenalidomide was administered orally on days 1 to 21 at doses as shown in Table 1. In the phase I trial, DLT was defined during cycle 1 as Grade 4 neutropenia or thrombocytopenia, Grade 4 infection or febrile neutropenia, Grade 3 infection or febrile neutropenia for > 7 days, treatment delays > 14 days, or other Grade 3 to 4 nonhematologic toxicity. DLT during cycle 1 led to study withdrawal. In cycles 2 and later in the phase I study and for patients in the phase II study, a new cycle could begin if the absolute

neutrophil count was $> 1000/\mu\text{L}$, platelets were $> 50,000/\mu\text{L}$, and all other toxicities had resolved to Grade 2. Dose reductions to 1 dose level below the patient's starting dose (see Table 1) were required in the event of treatment delays because of Grade 3 to 4 neutropenia or thrombocytopenia on day 1 of a cycle, Grade 3 or 4 neutropenia or thrombocytopenia at any time during a cycle, Grade 3 to 4 febrile neutropenia, or any Grade 3 to 4 non-hematologic toxicity. Electrocardiograms (ECGs) were required on days 1 and 5 of cycle 1 and on day 1 of cycles 2 to 4. For QTc prolongation > 450 ms at any time point, serum electrolyte levels (potassium, calcium, magnesium, and phosphorous) were evaluated and corrected. If repeat ECG after electrolyte replacement failed to correct the QTc prolongation, panobinostat was held for 3 days and ECG repeated. If the QTc remained > 450 ms after a 3-day dosing delay, panobinostat was discontinued; however, if the QTc was ≤ 450 ms panobinostat dosing was resumed at 1 lower dose level.

Women of reproductive potential enrolled in the study were required to have a negative pregnancy test 10 to 14 days before starting study therapy, 24 hours before to cycle 1 day 1, and every 28 days while receiving lenalidomide. All patients were required to take aspirin (81 or 325 mg) daily as thromboembolism prophylaxis and low molecular-weight heparin was recommended for patients intolerant of aspirin or at increased risk of venous thrombosis. Response was assessed using computed tomography (CT) scans of the chest, abdomen, and pelvis or positron emission tomography/CT after cycle 2 and every 4 cycles thereafter according to International Harmonization Criteria.¹⁴

Pharmacokinetics—Pharmacokinetic (PK) profiles of lenalidomide were obtained on cycle 1 day 1. Blood samples for PK analysis were collected at the following time points: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after lenalidomide administration on cycle 1 day 1. The 0-, 24-, and 48-hour samples were obtained before oral dosing of lenalidomide as well as panobinostat. Plasma concentrations of lenalidomide were measured using a validated high-performance liquid chromatography tandem mass spectrometry assay.¹⁵ PK parameters were estimated using non-compartmental analysis using Phoenix WinNonlin version 6.3. Statistical comparisons of plasma lenalidomide concentration between 24 and 48 hours was performed using Wilcoxon signed rank test using SigmaPlot 12.0 (Systat Software Inc).

Statistical Analysis

The phase I study was conducted using a standard 3 + 3 dose escalation design starting at dose level 1 (see Table 1). The MTD was defined as the highest dose at which no more than 1 of 6 enrolled patients experienced a DLT during cycle 1. When the recommended phase II dose was determined from the phase I study, a phase II trial was initiated to determine the ORR (CR+PR) per international response criteria¹⁴ with combined panobinostat and lenalidomide. A Simon minimax 2-stage design was used on the basis of previous single-agent studies of lenalidomide and panobinostat in which the ORR of 19% to 27% was described.^{8,10,16} We proposed that a combination of panobinostat and lenalidomide would be worthy of further study if the target ORR was $> 30\%$. We considered the regimen to be ineffective if the true ORR was $< 10\%$. These figures resulted in a Simon 2-stage minimax design of 16 and 25 HL patients, with an α of 0.10 and β of 0.10. If 1 or no responders were

seen in the first 16 evaluable patients, early termination of the study for lack of efficacy was planned. Evaluable patients were defined as those who completed at least 1 cycle of combined lenalidomide and panobinostat therapy.

In the final data analysis, summary statistics (ie, median and range for continuous variables and frequency for discrete data) were calculated for patient demographic and clinical characteristics, and toxicities. Progression-free survival (PFS) was calculated from the date of start of therapy to disease progression or death, whichever occurred first. If the patient did not have an event of disease progression nor died, informative censoring occurred at the date of the last available disease progression assessment. Overall survival (OS) was calculated from the date of start of therapy to death from any cause or the date of last follow-up. Patients who were still alive were censored at the last follow-up. Actuarial survival curves were estimated using the method of Kaplan-Meier. Estimated median with 95% confidence intervals (CIs) are reported.

Results

Patient Characteristics

Twenty-four patients (17 male) were enrolled. Twenty-three had cHL and 1 had LP HL. The median age was 45 (range, 22-72) years. Patients had received a median of 4 previous therapies (range, 2-13). Eleven (45.8%) patients were refractory to their most recent therapy and 22 patients (91.7%) had stage III to IV disease at study entry. Fifteen patients (62.5%) had a previous autologous stem cell transplantation, 1 patient (4.2%) had received previous allogeneic Epstein-Barr virus-directed cytotoxic T-cells, 1 patient had a previous syngeneic transplantation (4.2%), and 3 patients had previous autologous as well as allogeneic transplantations (12.5%). Fifteen patients (62.5%) had previously received brentuximab vedotin and 0 patients had previously received programmed cell death protein 1 inhibition with either pembrolizumab or nivolumab. Patient characteristics are detailed in Table 2.

Dose Escalation and Study Treatment

Eleven patients were enrolled in the phase I study. Three patients were initially treated at dose level 1 and 5 patients were treated at dose level 2. No dose-limiting toxicities were observed at dose levels 1 or 2; however, 2 patients treated at dose level 2 experienced Grade 4 neutropenia and thrombocytopenia for > 14 days during cycle 2. In addition, 3 of 5 patients treated at dose level 2 required dose reductions to dose level 1 during cycles 2 or 3. Therefore, 3 additional patients were treated at dose level 1 to ensure patient safety and this dose of lenalidomide 25 mg and panobinostat 15 mg became the recommended dose for the phase II study.

Thirteen patients were enrolled in the phase II study. Although according to the Simon 2-stage design 16 patients were required before interim analysis, this study closed early because of limited efficacy and slow accrual. In all 24 patients, the median number of cycles completed was 4 (range, 1-22). Thirteen patients required dose reductions for the following toxicities: neutropenia (n = 9), thrombocytopenia (n = 5), febrile neutropenia (n = 3), erythema nodosum (n = 1), transaminitis (n = 1), fatigue (n = 1), and lung infection (n = 1).

Eight patients received dose reduction from dose level 1 to dose level –1. One patient received a dose reduction from dose level 2 to dose level 1. Two patients received a dose reduction multiple times from dose level 2. Two patients received a dose reduction multiple times from dose level 1. Nine patients did not require dose reduction during their time in the study and all were eventually removed for progressive disease. However, the median number of cycles given to these patients was 2.

Response and Survival

In 24 evaluable patients who completed 1 or more cycles of combined panobinostat and lenalidomide, the ORR was 16.7% (2 CR and 2 PR). One additional patient enrolled in the study achieved a PR, however, this patient received lenalidomide therapy alone because of prolonged QTc on cycle 1 day 1 precluding panobinostat administration. Responses occurred in 1 patient in the phase I study and 3 patients in the phase II trial. One of the 2 patients with CRs occurred in a patient with LP HL who continued study therapy for 22 cycles and stopped protocol therapy to undergo elective coronary artery bypass grafting. This patient remains in CR at time of report, which is > 2 years after withdrawing from protocol. The other 3 responses occurred in patients with cHL who continued therapy until disease progression for 3 and 6 cycles or until fungal pneumonia after 3 cycles required trial discontinuation. Of the 3 cHL patients who responded and were included in analysis, the range of response duration was 4.0 to 6.8 months. Eleven patients had SD and the median duration of SD was 3.7 months. A waterfall plot for patients' response is shown in Figure 1.

Five patients died including 4 because of disease progression and 1 from treatment-related infection, right upper lobe pneumonia, with prolonged neutropenia 32 days after cycle 3 on day 1. Median PFS was 3.8 months (95% CI, 1.8-5.9; range, 0.7-39.3 months; Figure 2). Median OS was 16.4 months (95% CI, 7.0-19.3 months; range, 1.1-39.3 months).

Toxicities

Twenty-three patients discontinued protocol therapy because of disease progression (n = 17) or adverse events (n = 6), including Grade 4 neutropenia/thrombocytopenia in 3 patients, unexplained altered mental status after drug dosing on cycle 1 day 1 in 1 patient, fungal pneumonia requiring long-term voriconazole treatment with concurrent disease progression in 1 patient, and elective coronary artery bypass grafting in a patient with known coronary artery disease before study enrollment (n = 1).

Grade 3 to 4 toxicities in all 24 patients are summarized in Table 3 and included neutropenia (58.3%, 14 patients), thrombocytopenia (41.7%, 10 patients), lymphopenia (25.0%, 6 patients), febrile neutropenia (25.0%, 6 patients), and hypophosphatemia (8.3%, 2 patients). Cardiac toxicity was absent in this study because 1 participant was enrolled in the study but never received panobinostat because of QTc prolongation before dosing in cycle 1 on day 1. This patient proceeded with lenalidomide therapy alone.

Pharmacokinetics

Lenalidomide PK data were obtained from 14 patients, and the plasma concentration-time profiles are shown in Figure 3. Lenalidomide was rapidly absorbed and reached maximum

plasma concentration 0.75 to 3 hours after administration. Blood samples were also collected at 48 hours to compare lenalidomide trough levels with (day 1) and without (day 2) coadministration of panobinostat. The mean concentration at 48 hours ($40.5 \pm 33.0 \mu\text{M}$) was slightly higher, but not statistically different, than that at 24 hours ($30.5 \pm 27.2 \mu\text{M}$; $P < .05$). Noncompartmental PK parameter estimates are summarized in Table 4.

Discussion

On the basis of the promising single-agent efficacy and prolonged duration of responses observed with single-agent lenalidomide as well as panobinostat in patients with relapsed and refractory HL, we conducted this study to examine the safety and efficacy of combination therapy with these 2 agents. In this trial, Grade 3 to 4 neutropenia was the primary toxicity that occurred in 14 patients (58.3%) of the patients and led to dose reductions in 7 patients (29.2%). Although no dose-limiting toxicities were observed, prolonged neutropenia and thrombocytopenia during cycle 2 in 2 patients and requirements for dose reductions in 3 of 5 patients treated with 20 mg panobinostat and 25 mg lenalidomide led us to recommend 15 mg panobinostat and 25 mg lenalidomide for further evaluation in the phase II trial. In the phase II study, 13 patients were enrolled with only 3 responses (1 CR and 2 PR) of 5, 3, and 1 month duration, respectively, leading to premature closure of this trial.

Previously published single-agent efficacy of lenalidomide in this population is 14% to 50%^{7,8} and similarly, single-agent efficacy of panobinostat in patients with HL is 27% to 58%.^{10,16} With an ORR of 16.7% in all 24 evaluable patients in this trial and an ORR of 23% in the 13 patients in the phase II study, our study of combined lenalidomide and panobinostat at best showed an ORR comparable with either agent alone. Furthermore, the median PFS of 3.8 months with the combination was no better than the 4 to 6.1 months observed with the single agents. Therefore, with the added risk of myelosuppression with the combination, we would not recommend combined therapy with these 1 agents on the basis of the findings from this trial. Greater disease burden is an unlikely explanation for the poor response rate shown with the combination because most patients in the single-agent lenalidomide and panobinostat trials had previous autologous transplantation (87% and 100%, respectively) and were equally heavily pretreated with a median of 4 previous therapies. Additionally, 55% and 74% of patients had refractory disease before single-agent lenalidomide and panobinostat, respectively, similar to the 46% refractory rate in the current trial. Last, unlike the previous single-agent studies in which most patients achieved some tumor reduction (74% with panobinostat) and in which responses were often delayed with 33% to 82% of patients achieving meaningful disease control (CR + PR + SD), only 3 of 11 patients in this combination study with SD continued in the study for longer than 4 cycles. Although this study does not provide this information directly, it is unlikely that continuation at a lower dose would lead to a meaningful improved result in patients at dose level 1 as well as dose level 2 who did not require dose reductions, and were withdrawn from the study because of progressive disease early in the treatment course.

In single-agent panobinostat trials, thrombocytopenia was the most common toxicity ranging from 77% to 85%,^{10,16} with Grade 3 to 4 neutropenia only occurring in 8% to 27%.^{10,16}

When using 25 mg of lenalidomide in patients with heavily pretreated HL, Grade 3 to 4 neutropenia was observed in 0% to 47% and Grade 3 to 4 thrombocytopenia was less frequent at 0% to 28%.^{7,8} Unexpectedly with thrice weekly panobinostat dosing in this combination trial, the primary toxicity was not thrombocytopenia as initially expected, but neutropenia. In the single-agent phase II trial with panobinostat in HL, doses of 40 mg 3 times a week were used and perhaps the lower doses of 15 to 20 mg limited the efficacy observed in this study. However, this increased panobinostat dose is not approved by the US Food and Drug Administration (FDA) for this indication and alternatively the FDA-approved panobinostat dose in combination therapy with bortezomib and dexamethasone for multiple myeloma patients is 20 mg.¹⁷ Consideration is given to decreasing the doses of lenalidomide to increase the panobinostat dose, but we believe this is not likely to have too much of a significant clinical effect in light of the continued toxicity risk.

In a recently published phase I study of panobinostat with everolimus in patients with relapsed/refractory lymphoma,¹⁸ the MTD was panobinostat 20 mg 3 times a week and everolimus 10 mg daily, with DLT consisting of thrombocytopenia. In this trial, Grade 3 to 4 thrombocytopenia was 64% and neutropenia was 47%, similar to the 42% thrombocytopenia and 58% neutropenia rates with panobinostat and lenalidomide. Despite the lower dose of panobinostat, an ORR of 43% was observed with combined panobinostat and everolimus in 14 heavily pretreated patients with HL. This ORR exceeds the single-agent activity of panobinostat as well as everolimus in HL for which ORR of 27% and 37%, respectively, has been described.^{10,19} Why the combination of 2 active single agents in our study led to lower than expected responses is not clear but raises the possibility of an unknown antagonistic effect when lenalidomide is combined with histone deacetylase inhibitors.

Panobinostat as well as lenalidomide are known substrates for P-glycoprotein^{20,21} and we therefore evaluated the possibility of a PK drug interaction in this combination study. The plasma PK data obtained from this study showed lenalidomide parameter estimates were similar to the values reported previously in lenalidomide single-agent studies,^{22,23} and therefore the surprisingly low ORR observed in this trial cannot be explained by altered lenalidomide plasma PKs. Lenalidomide is considered to be a weak permeability glycoprotein substrate, has not been shown previously to alter PK of other coadministered drugs, and was therefore unlikely to have altered panobinostat PK in this study. Nonetheless, PK data for panobinostat were not collected, and we therefore cannot confirm this. In this study, 2 patients with higher lenalidomide exposure of 9.28 and 16.54 h/μmol/L did show greater tumor reduction rates of 93.0% and 62.3%, respectively, suggesting a possible association between drug exposure and clinical responses; however, it is unlikely that the lenalidomide doses could have been escalated beyond the 20 to 25 mg used in this study because of worsening myelosuppression and this is the standard dose for patients with lymphoma.

Conclusion

In this phase I/II trial of panobinostat and lenalidomide, the recommended phase II doses of lenalidomide and panobinostat in combination were 20 mg on days 1 to 21 and 15 mg 3 times per week for 28-day cycles, respectively. However, with an ORR of only 16.7% and

Grade 3 to 4 neutropenia and febrile neutropenia observed in 58% and 25% of patients, respectively, there is no advantage using this combination over single-agent treatment in patients with relapsed or refractory cHL. On the basis of the results of this trial, further evaluation of combined panobinostat and lenalidomide is not warranted; although combinations of other agents including everolimus, checkpoint inhibitors, or B-cell receptor pathway inhibitors with either panobinostat or lenalidomide might prove to be more effective. In addition, because the only long-term responder in this trial was a patient with LP HL, this unique subtype of HL should be included in future trials with these novel agents.

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Clinical Practice Points

- Lenalidomide and panobinostat have shown single-agent efficacy of 14% to 50% and 27% to 58%, respectively, in patients with relapsed or refractory HL and are considered management options for this patient population.
- In this study, the activity of combined lenalidomide and panobinostat in relapsed or refractory HL was 16.7%, lower than the ORR with either drug alone and does not warrant further study.
- This study showed that the PK profile of lenalidomide does not change when given in combination panobinostat.
- When combined, panobinostat and lenalidomide are associated with significant risks of neutropenia, thrombocytopenia, and infection, and led to dose modifications in most patients.
- One patient with LP HL had a durable response after 22 cycles of combined lenalidomide and panobinostat treatment, suggesting that both of these agents should be evaluated further in this unusual subtype of HL.

Figure 1.
Response Rates

Figure 2.
Progression-Free Survival

Figure 3.
Plasma Lenalidomide Concentrations Over Time

Table 1

Phase I Dose Escalation and Treatment Schema

Dose Level	Lenalidomide	Panobinostat
-4	5 mg/d 1-7, weeks 1, 2, and 3	5 mg/d 1, 3, and 5; weeks 1 and 3 only
-3	10 mg/d 1-7, weeks 1, 2, and 3	5 mg/d 1, 3, and 5; weeks 1 and 3 only
-2	15 mg/d 1-7, weeks 1, 2, and 3	10 mg/d 1, 3, and 5; weeks 1 and 3 only
-1	20 mg/d 1-7, weeks 1, 2, and 3	15 mg/d 1, 3, and 5; weeks 1 and 3 only
1	25 mg/d 1-7, weeks 1, 2, and 3	15 mg/d 1, 3, and 5; weeks 1, 2, 3, and 4
2	25 mg/d 1-7, weeks 1, 2, and 3	20 mg/d 1, 3, and 5; weeks 1, 2, 3, and 4

The doses of study drug associated with each dosing level. One cycle = 28 days.

Table 2

Patient Characteristics (n = 24)

Characteristic	Value	%
Age		
Median age (range)	45 (22–72)	
Age ≥ 65 y	4	16.7
Sex		
Male	17	70.8
Female	7	29.2
HL Subtype		
cHL	23	95.8
LP HL	1	4.2
Number of Previous Therapies		
Median (range)	4 (2–13)	
4	15	62.5
10	2	8.3
Stage III–IV Disease at Time of Enrollment	22	91.7
Refractory to Last Therapy	11	45.8
Previous ASCT	15	62.5
Previous Brentuximab Vedotin	15	62.5
Previous PD-1 Inhibition	0	0.0
Previous ASCT and Allo-SCT	3	12.5
Ann Arbor Stage at Study Entry		
I–II	1	4.2
III–IV	23	95.8
B-Symptoms	3	12.5
Bone Marrow Involvement	1	4.2
Bulky Disease		
>5 cm	3	12.5
>10 cm	0	0.0

Values are presented as n except where otherwise noted.

Abbreviations: Allo-SCT = allogeneic stem cell transplantation; ASCT = autologous stem cell transplantation; cHL = classical Hodgkin lymphoma; LP HL = lymphocyte-predominant Hodgkin lymphoma; PD1 = programmed cell death protein 1.

Table 3

Grade 3 to 5 Toxicity Profile

Toxicity	Patients With Grade 3-5 Toxicity	
	n	%
Hematologic		
Thrombocytopenia	10	41.7
Neutropenia	14	58.3
Lymphopenia	6	25.0
Nonhematologic		
Constitutional		
Fatigue	1	4.2
Infectious		
Febrile neutropenia ^a	6	25.0
Infection without neutropenia ^b	3	12.5
Metabolic		
Hypokalemia	2	8.3
Hyponatremia	1	4.2
Hypophosphatemia	2	8.3
Hypocalcemia	1	4.2
Hypoalbuminemia	1	4.2
Dehydration	2	8.3
Neurologic		
Altered mental status	1	4.2
Gastrointestinal		
Hyperbilirubinemia/transaminitis	3	12.5
Nausea/vomiting	1	4.2
Dermatologic		
Rash ^c	1	4.2
Immune		
GVH	1	4.2

^aFebrile neutropenia included 1 case of death (Grade 5) related to infection.

^bInfection without neutropenia included 1 case of disseminated zoster (Grade 3) and 1 case of cholangitis (Grade 3).

^cRash was biopsy proven erythema nodosum (Grade 3).

Table 4

Pharmacokinetic Parameter Estimates of Lenalidomide After Oral Administration of 25 mg (n = 14)

Pharmacokinetic Parameter	gMean	SD
HL_Lambda_z, h	3.93	1.38
Tmax, h	1.42	0.78
Cmax, µmol/L	1.51	0.60
AUCINF_pred, h/µmol/L	7.80	3.90
V/F, L	70.13	34.4
CL/F, L/h	12.35	5.7

Abbreviations: AUCINF_pred = area under the curve from dosing time extrapolated to infinity, based on last predicted concentration; CL/F = Clearance/Fraction absorbed; Cmax = maximum plasma concentration; gMean = geometric mean; HL_Lambda_z = terminal half-life ($\ln(2)$ /terminal slope); Tmax = time of maximum observed concentration; V/F = Clearance/Fraction absorbed.