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A Phase I Study to Assess the Safety and Pharmacokinetics of Single-agent Lorvotuzumab Mertansine (IMGN901) in Patients with Relapsed and/or Refractory CD–56-positive Multiple Myeloma

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Abstract

Lorvotuzumab mertansine, a unique antibody–drug conjugate targeting CD56, is frequently expressed on multiple myeloma cells. The present phase I trial of the single agent describes the maximum tolerated dose, safety, and initial efficacy to aid future drug development.

Background: Despite therapeutic advancements that have significantly improved outcomes in multiple myeloma (MM), it remains an incurable disease. Patients with relapsed and/or refractory MM have an aggressive disease course, with inferior outcomes, necessitating the need for agents with novel therapeutic mechanisms. We present the results of a completed phase I trial of single-agent lorvotuzumab mertansine, a unique antibody-drug conjugate targeting CD56, which is frequently expressed in MM.

Patients and Methods: Thirty-seven patients with relapsed MM were enrolled in a dose-escalation phase I clinical trial to determine the maximum tolerated dose of lorvotuzumab mertansine (112 mg/m^2), followed by an expansion phase at the maximum tolerated dose.

Results: Despite a high proportion of patients with relapsed and/or refractory MM (56.8%), stable disease or better was noted in 42.9% of patients, and these patients had a long duration of

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response (median, 15.5 months). The adverse event profile was favorable, with a low incidence of grade 3/4 adverse events and no infusion-related reactions. No humoral responses were detected against the study drug.

Conclusion: This completed phase I trial of single-agent lorvotuzumab mertansine provides ample evidence of safety and signals of clinical activity for this agent, warranting its further clinical development as part of combination regimens for the management of MM.

Keywords

Antibody-drug conjugate; Drug-development; Efficacy; Immunotherapy; Monoclonal antibody

Introduction

Multiple myeloma (MM) is the most common primary malignancy of the bone marrow and the second most common hematologic malignancy, with approximately 30,000 new cases diagnosed in the United States in 2017.[1] MM is characterized by uncontrolled proliferation of plasma cells in the bone marrow leading to paraprotenemia and/or proteinuria, resulting in bone marrow failure, kidney dysfunction, pathologic fractures, or recurrent infections secondary to immunoparesis as the primary morbidity.[2–5] Several advances in therapeutic options and supportive care have led to improved survival for patients with MM.[6–10] However, MM remains thus far an incurable disease, and even patients who experience a prolonged, high-quality response to initial combination novel therapies with or without a stem cell transplant, will typically relapse with disease that is refractory to available agents.[4,10] The prognosis of patients who become resistant to novel therapeutic agents, particularly with respect to overall survival, is extremely poor.[11] Therefore, development of new agents with unique mechanisms of action remains an important focus of research for the treatment of patients with relapsed and relapsed-refractory multiple myeloma (RRMM).

In recent years, the United States Food and Drug Administration approval of monoclonal antibodies (MoAbs) for the treatment of RRMM has revolutionized immunotherapy-based management in MM.[12–14] A number of other monoclonal antibodies against surface antigens on the plasma cell and signaling molecules in the tumor microenvironment are currently under development.[4,11] Similarly, the investigation of antibody-drug conjugates (ADCs), complex engineered molecules that consist of an antibody, directed toward tumor-associated antigens, conjugated to potent cytotoxic drugs, are showing encouraging signs of efficacy in ongoing phase I and II clinical trials in MM and other lymphoid malignancies.[15–17] One such agent, lorvotuzumab mertansine (IMGN901), is an ADC of the anti-CD56 antibody lorvotuzumab (huN901), bound via disulfide linkage to the cytotoxic maytansinoid effector molecule DM1.[18] The target of this ADC, the CD56 antigen, is primarily expressed in cells of neuroendocrine origin, as well as in natural killers and some T cell subtypes, but its aberrant expression is found in several solid organ and hematologic malignancies, including MM.[18–20] Because CD56 is expressed on 75% of myeloma cells but on less than 15% of normal cells, it is not only a useful marker of disease but also an attractive therapeutic target. Based on promising in vitro and in vivo preclinical data, phase I studies using lorvotuzumab mertansine have been conducted for both solid tumors and hematologic malignances, including phase I studies in RRMM, both as monotherapy and in combination

with lenalidomide and dexamethasone, preliminary results from which were presented previously.[21,22] Here, we present results from the phase I clinical trial to assess the safety, tolerability, and pharmacokinetics (PK) of lorvotuzumab mertansine when administered as monotherapy to patients with CD56-positive ($CD56^+$) relapsed or RRMM.

Patients and Methods

Trial Design

The clinical trial was an open-label phase I study (NCT00346255) with the primary objective of determining the maximum tolerated dose (MTD) of lorvotuzumab mertansine. Secondary objectives included assessment of toxicities, PK, and initial evidence of antitumor activity. Each cycle of treatment consisted of 21 days, where patients received an infusion of lorvotuzumab mertansine on days 1 and 8 followed by a 14-day treatment-free interval. Premedication included steroids on the day prior to infusion, along with acetaminophen, steroids, and diphenhydramine on the day of infusion. The starting dose was 40 mg/m^2, with escalation to 60, 75, 90, 112, and 140 mg/m^2. Dose escalation followed a standard 3 + 3 design, such that if 1 of 3 patients experienced a dose-limiting toxicity (DLT) at a given dose level, the cohort was to be expanded to 6 patients, and if at least 2 patients experienced a DLT, the MTD was reached with no further escalation permitted. The MTD was determined as the dose level prior to that resulting in intolerable toxicity. Intra-patient dose escalations were not allowed in this study. All patients signed informed consent before initiation of study participation, and the study received approval from institutional board at the participating sites.

Patient Selection

Adult patients with $CD56^+$ RRMM with at least 1 prior line of therapy were enrolled on the dose-escalation portion of the trial. After the MTD was defined, patients who had received 1, but no more than 6, prior lines of therapy were eligible to enroll into the expansion phase. Additionally, patients had to have an Eastern Cooperative Oncology Group performance status of ≤ 2, an expected survival ≥ 12 weeks, and adequate organ function including bone marrow (absolute neutrophil count > 1000 cells/mm^3, hemoglobin > 8.5 g/dL, platelet count ≥ 75,000/mm^3), liver (serum alanine or aspartate transaminase levels < 3 × upper limit of normal [ULN]; total bilirubin ≤ 1.5 × ULN), pancreas (amylase and lipase levels within the ULN), kidney (creatinine < 2 mg/dL), and cardiac (left ventricular ejection fraction ≥ lower limit of normal) function. Patients with significant concomitant infections or having ≥ grade 3 or painful grade 2 peripheral neuropathy were excluded.

Endpoints and Assessments

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology for Adverse Events, version 3.0. DLTs occurring in cycle 1 were used to determine the MTD. During cycle 1, evaluations were performed on days 1 through 5 and then on days 8, 9, and 15. During cycle 2 and beyond, patients had evaluations performed on days 1, 2, 8, and 15. Response to treatment was assessed after each cycle of therapy by the treating physicians, using the European Group for Bone Marrow Transplant criteria.[23] Patients came off study for disease progression or intolerable toxicities. Follow-up survival

information was collected every 3 months until death or 3 years from first study treatment, whichever occurred earlier.

PK studies for lorvotuzumab mertansine included blood and urine samples. Blood levels of the drug were determined using a qualified enzyme-linked immunosorbent assay on days 1 to 5, days 8 to 9, and day 15 of cycles 1, 2, and 5. On the same schedule, plasma was also evaluated for the presence of humoral responses against the huN901 antibody component (human anti-human antibody) or against the DM1 component (human anti-drug antibody). The PK profile in urine was determined by measuring levels of free drug on 24-hour urine samples collected over day 1 to 2 and day 2 to 3 in cycles 1 and 5.

Statistical Analysis

The intent-to-treat population was defined as all patients who received 1 or more doses of study drug, and all safety analyses were conducted on this population, whereas the efficacy evaluable population was defined as all the patients from the intent-to-treat population with ≥ 1 post-baseline efficacy assessment. Statistical analysis was descriptive in nature, except for the survival analysis, where the Kaplan-Meier method was used for the median time estimates.

Results

A total of 37 patients with $CD56^+$ MM were enrolled in this study. Patient demographics and baseline characteristics are summarized in Table 1. The median age for all patients was 61 years (range, 39–85 years), and the median time since diagnosis in all patients was 5.2 years (range, 0.8–10.8 years). The majority (70.3%) of the patients had International Staging System stage III disease, and 56.8% had RRMM. During the dose-escalation phase, 3 patients each were enrolled in each of the dose escalation cohorts (40 mg/m^2, 60 mg/m^2, 75 mg/m^2, 90 mg/m^2, and 112 mg/m^2), whereas 6 patients were enrolled in the 140 mg/m^2 cohort. Two patients experienced DLTs at the 140 mg/m^2 dose level (1 case each of grade 3 fatigue and grade 3 renal failure), and 112 mg/m^2 was established as the MTD. Sixteen additional patients were subsequently dosed at this level as part of the expansion phase. All 37 patients received at least 1 dose of the study drug and had at least 1 valid post-baseline PK sample collected. Thirty-five of the 37 patients completed the first study-related response assessment, scheduled at the end of the second cycle, comprising the efficacy evaluable cohort.

The median duration of treatment was 1.6 months (range, 1–17.6 months). Most patients (81%) received > 1 cycle of treatment, with 43% receiving ≥ 4 cycles. Among the 37 patients treated, 2 patients experienced a DLT during cycle 1 in the 140 mg/m^2 cohort (1 with grade 3 fatigue and 1 with grade 3 kidney dysfunction). Based on the DLT rules, the next lower level of 112 mg/m^2 was determined to be the MTD. All grade treatment-emergent AEs (TEAEs) that were considered related to the study drug were seen in 33 (89%) of the 37 patients. These included headache (32%), fatigue (32%), paresthesia (24%), increased serum aspartate transaminase (22%), peripheral neuropathy (22%), diarrhea (19%), constipation (16%), and decreased appetite (16%). Of note, the incidence of study drug-related peripheral neuropathy was 51% (19 of 37 patients). Grade

3 to 4 study drug-related TEAEs by treatment cohort and overall are shown in Table 2. TEAEs resulted in study drug discontinuation in 9 patients, with the most common cause being peripheral neuropathy (n = 4; all in 112 mg/m^2 cohort). Other TEAEs that led to study drug discontinuation were hip fracture (n = 1; 90 mg/m^2 cohort); hypercalcemia (n = 1; 112 mg/m^2 cohort); and fatigue, myalgia, and renal failure (n = 1 each; all in140 mg/m^2 cohort). There were 2 on-study deaths, both owing to disease progression.

Among the 35 patients evaluable for response, a partial response (PR) was noted in 2 (5.7%) patients and an additional 4 (11.4%) patients had a minor response (MR). None of the patients achieved a very good PR or complete response. The most common best response achieved with study treatment was stable disease (no change), seen in 15 (42.9%) patients. The rates of best response to study therapy by treatment cohort and overall are shown in Table 3. Among the 6 patients who achieved PR or MR as their best response, the median duration of response was 61.9 weeks. The median progression-free survival in the evaluable population was 26.1 weeks (range, 1–89 weeks).

All 37 patients were included in the PK-evaluable population in the trial. The area under the curve of lorvotuzumab mertansine increased with increasing dose, with a half-life of approximately 1 day in the 112 mg/m^2 cohort. The plasma concentration of huN901 antibody also increased proportionately to the dose administered, with a short half-life of 1.5 days, suggesting antigen-mediated clearance of the antibody to be a major component of the study drug elimination. Plasma levels of DM1 were nearly undetectable, and its proportional increase in urine with increasing dose indicated that DM1 is rapidly cleared upon release from IMGN901. There were no humoral immune responses (human anti-human antibody or human anti-drug antibody) detected against IMGN901.

Discussion

Lorvotuzumab mertansine is a novel antibody-drug conjugate, which has not been previously investigated in MM. This is the first clinical trial of this anti-CD56 targeting agent in humans. Here, we report results of our completed phase I study of lorvotuzumab mertansine, which was conducted to establish the MTD of this compound in patients with RRMM. The MTD was established at 112 mg/m^2 with a manageable safety profile. In addition, at this dose, we also observed some initial signs of clinical benefit and anti-myeloma effects.

Among MoAbs, 2 with a unique mechanism of action are now approved for treatment of RRMM. These include daratumumab and elotuzumab.[24–26] Although daratumumab did show single-agent clinical activity, elotuzumab single-agent activity was modest and comparable with that noted in this study with lorvotuzumab mertansine.[12–14,27] The overall clinical benefit of elotuzumab could only be realized in a combination regimen strategy with existing anti-myeloma agents.[10,14] The clinical profiles of patients enrolled on the phase I, single-agent trials for both these MoAbs were very similar to those enrolled in our current clinical trial with lorvotuzumab mertansine. In general, patients were heavily pretreated, with advanced-stage disease, and all had relapsed disease, with a sub-stantial proportion having RRMM.

Although the median duration of treatment was 1.6 months, nearly one-half the patients received the study drug for more than 4 months. The side-effect profile was quite manageable, with no serious AEs. Although no infusion-related reactions were noted in the study as compared with those that have been noted with other anti-MM MoAbs, including daratumumab and elotuzumab, interestingly, peripheral neuropathy was seen more commonly (51% of the patients) with lorvotuzumab mertansine as compared with these other agents, although the majority of it was low grade (grade ≤ 2).[14,25]

Disease stabilization was the most frequently observed clinical response in patients treated with lorvotuzumab mertansine (42.9%), despite refractory disease being present in approximately 57% of the patients (Table 1). Additionally, 17% patients saw an objective decrease in their MM paraprotein, meeting the criteria of MR or PR. These early signals of efficacy are below those observed with recent single-agent trials in MM, such as carfilzomib and daratumumab, but comparable with others, including elotuzumab and panobinostat.[26,28–31] Patients who experienced any clinical benefit had, on average, a long duration of response (15.5 months) and median progression-free survival (6.5 months), underscoring the long-term safety as well as efficacy of this agent. This is similar to other immunologic agents that have shown a long duration of benefit in responding patients.[28] Because CD56 expression may be lost in patients with more advanced disease, lorvotuzumab mertansine may prove more useful as part of earlier lines of therapy for MM.[32,33] Our continued enthusiasm regarding lorvotuzumab mertansine comes from the fact that, in the era of targeted therapy exploiting the immunologic basis of treatment, the initial high single-agent response rate may not be the only sign of efficacy. This is evident from the observation that several therapeutic agents have gone on to receive United States Food and Drug Administration approval despite poor single-agent clinical activity.[26,29] Our study met the most important objective of defining the MTD and single-agent toxicity profile. In addition, the initial efficacy results, albeit modest in MM, warrant further investigation through combination therapeutic strategies. A subsequent trial of the combination of lorvotuzumab mertansine with lenalidomide and dexamethasone has recently been completed in patients with relapsed or RRMM, with preliminary results reported.[22]

The current state of novel drug development in MM is focused on development of unique therapeutic targets and mechanisms of action of agents to exploit disease biology and achieve clinical benefit for patients.[11] This strategy has led to improved outcomes of patients even beyond the cornerstone drug classes of immunomodulatory agents and proteasome inhibitors. Considering this, lorvotuzumab mertansine provides a novel therapeutic option with a unique mechanism that has shown early signs of clinical activity in patients with RRMM. In this regard, lorvotuzumab mertansine warrants further development in order to understand the full potential and benefit from this novel class of agents.

Disclosure

S.A. has received research funding from Pharmacyclics and is a consultant with Celgene, Amgen, Takeda, and Janssen. K.R.K. has received honorarium from Seattle Genetics, Janssen, Novartis, and Gilead. S.J. is a consultant with Celgene, Bristol-Myers Squibb, Novartis, and Merck and has been on the speaker's bureaus for the Multiple Myeloma Research Foundation and Medicom. J.W. is a consultant with Amgen, Celgene, Janssen, Novartis, Squibb, and Takeda. M.K. is employed by Immunogen, Inc. The remaining authors have stated that they have no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67:7–30. [PubMed: 28055103]
2. Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica 2015; 100:107–13. [PubMed: 25344526]
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78:21–33. [PubMed: 12528874]
4. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia 2016; 30:1005–17. [PubMed: 26710887]
5. Smith D, Yong K. Multiple myeloma. BMJ 2013; 346:f3863. [PubMed: 23803862]
6. Ailawadhi S, Aldoss IT, Yang D, et al. Outcome disparities in multiple myeloma: a SEER-based comparative analysis of ethnic subgroups. Br J Haematol 2012; 158: 91–8. [PubMed: 22533740]
7. Ailawadhi S, Frank RD, Sharma M, et al. Trends in multiple myeloma presentation, management, cost of care, and outcomes in the Medicare population: a comprehensive look at racial disparities. Cancer 2018; 124:1710–21. [PubMed: 29360160]
8. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv 2017; 1:282–7. [PubMed: 29296944]
9. Raje NS, Yee AJ, Roodman GD. Advances in supportive care for multiple myeloma. J Natl Compr Canc Netw 2014; 12:502–11. [PubMed: 24717569]
10. Dingli D, Ailawadhi S, Bergsagel PL, et al. Therapy for relapsed multiple myeloma: guidelines from the Mayo stratification for myeloma and risk-adapted therapy. Mayo Clin Proc 2017; 92:578–98. [PubMed: 28291589]
11. Chim CS, Kumar SK, Orlowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. Leukemia 2018; 32:252–62. [PubMed: 29257139]
12. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375:754–66. [PubMed: 27557302]
13. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375:1319–31. [PubMed: 27705267]
14. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015; 373:621–31. [PubMed: 26035255]
15. Robak P, Robak T. Management of multiple myeloma with second-generation antibody-drug conjugates. BioDrugs 2016; 30:87–93. [PubMed: 26927803]
16. Robak T, Robak E. Current phase II antibody-drug conjugates for the treatment of lymphoid malignancies. Expert Opin Investig Drugs 2014; 23:911–24.
17. Chari RV, Miller ML, Widdison WC. Antibody-drug conjugates: an emerging concept in cancer therapy. Angew Chem Int Ed Engl 2014; 53:3796–827. [PubMed: 24677743]
18. Whiteman KR, Johnson HA, Mayo MF, et al. Lorvotuzumab mertansine, a CD56-targeting antibody-drug conjugate with potent antitumor activity against small cell lung cancer in human xenograft models. MAbs 2014; 6:556–66. [PubMed: 24492307]
19. Shah MH, Lorigan P, O'Brien ME, et al. Phase I study of IMGN901, a CD56-targeting antibody-drug conjugate, in patients with CD56-positive solid tumors. Invest New Drugs 2016; 34:290–9. [PubMed: 26961907]
20. Lambert JM, O'Leary J, Whiteman K, Goldmacher V. Targeting CD56 (NCAM)-expressing neoplasms with lorvotuzumab mertansine. In: Phillips GL, ed. Antibody-drug conjugates and immunotoxins: from pre-clinical development to therapeutic applications, cancer drug discovery and development. New York: Business Media; 2013:273–93.
21. Chanan Khan AA, Jagannath S, Munshi NC, et al. Phase I study of huN901-DM1 (BB-10901) in patients with relapsed and relapsed/refractory CD56-positive multiple myeloma. Blood Adv 2007; 110:1174 (abstract).

22. Berdeja JG, Ailawadhi S, Niesvizky R, et al. Phase I study of lorvotuzumab mertansine (IMGN901) in combination with lenalidomide and dexamethasone in patients with CD56-positive relapsed or relapsed/refractory mulitple myeloma - a preliminary safety and efficacy analysis of the combination. Blood Adv 2010; 116:1934 (abstract).

23. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998; 102:1115–23. [PubMed: 9753033]

24. Weisel K Spotlight on elotuzumab in the treatment of multiple myeloma: the evidence to date. Onco Targets Ther 2016; 9:6037–48. [PubMed: 27785050]

25. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016; 387:1551–60. [PubMed: 26778538]

26. Wolf JL, Siegel D, Goldschmidt H, et al. Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. Leuk Lymphoma 2012; 53:1820–3. [PubMed: 22288662]

27. Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. Blood 2016; 127:713–21. [PubMed: 26631116]

28. Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016; 128:37–44. [PubMed: 27216216]

29. Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. Blood 2012; 120:552–9. [PubMed: 22184404]

30. Vij R, Siegel DS, Jagannath S, et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol 2012; 158:739–48. [PubMed: 22845873]

31. Jagannath S, Vij R, Stewart AK, et al. An open-label single-arm pilot phase II study (PX-171–003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2012; 12:310–8. [PubMed: 23040437]

32. Dahl IM, Rasmussen T, Kauric G, Husebekk A. Differential expression of CD56 and CD44 in the evolution of extramedullary myeloma. Br J Haematol 2002; 116: 273–7. [PubMed: 11841427]

33. Pellat-Deceunynck C, Barille S, Puthier D, et al. Adhesion molecules on human myeloma cells: significant changes in expression related to malignancy, tumor spreading, and immortalization. Cancer Res 1995; 55:3647–53. [PubMed: 7543019]

Clinical Practice Points

- Treatment of relapsed and refractory MM has been transformed significantly in the recent past; however, the outcomes for patients with disease refractory to current agents have remained poor.
- Thus, drug development with agents in novel therapeutic classes that are safe and efficacious is necessary for patient outcomes to continue to improve.
- We present data from a phase I trial of single-agent lorvotuzumab mertansine, an antibody–drug conjugate targeting CD56, commonly expressed on MM cells.
- The agent was found to be safe, we were able to define the maximum tolerated dose, and it showed initial signs of efficacy with an impressive median response of 15.5 months.
- The safety and efficacy signal from this agent warrants further clinical development as a combination as a unique therapeutic option for patients with MM.

Table 1

Patient Characteristics

Characteristic	Lorvotuzumab Mertansine Dose Level (mg/m^2), n (%)						
	40 (N = 3)	**60 (N = 3)**	**75 (N = 3)**	**90 (N = 3)**	**112 (N = 19)**	**140 (N = 6)**	**Overall (N = 37)**
Gender							
Male	2 (66.7)	0	1 (33.3)	2 (66.7)	13 (68.4)	3 (50)	21 (56.8)
Female	1 (33.3)	3 (100)	2 (66.7)	1 (33.3)	6 (31.6)	3 (50)	16 (43.2)
Age, y							
Median	66	69	55	58	61	64	61
Range	61–67	61–71	49–60	57–69	39–85	44–82	39–85
Race							
Caucasian	1 (33.3)	3 (100)	2 (66.7)	3 (100)	19 (100)	6 (100)	34 (91.9)
African American	1 (33.3)	0	1 (33.3)	0	0	0	2 (5.4)
Other	1 (33.3)	0	0	0	0	0	1 (2.7)
Median time since initial diagnosis, mos	86.2	46.2	47	69.3	63.6	56.0	63.4
ISS stage at diagnosis							
I	1 (33.3)	0	0	0	5 (26.3)	0	6 (16.2)
II	0	0	0	0	4 (21.1)	1 (16.7)	5 (13.5)
III	2 (66.6)	3 (100)	3 (100)	3 (100)	10 (52.6)	5 (83.3)	26 (70.3)
Disease status at study enrollment							
Relapsed	1 (33.3)	1 (33.3)	0	0	10 (52.6)	4 (66.7)	16 (43.2)
Relapsed and refractory	2 (66.7)	2 (66.7)	3 (100)	3 (100)	9 (47.4)	2 (33.3)	21 (56.8)
Number of prior lines of therapy							
2	0	0	0	0	1 (5.3)	1 (16.7)	2 (5.4)
3	0	0	0	0	5 (26.3)	1 (16.7)	6 (16.2)
>3	3 (100)	3 (100)	3 (100)	3 (100)	13 (68.4)	4 (66.7)	29 (78.4)
Prior radiation therapy	0	3 (100)	2 (66.7)	2 (66.7)	8 (42.1)	2 (33.3)	17 (45.9)

Abbreviation: ISS = International Staging System.

Table 2

Grade 3/4 Treatment-emergent Adverse Events Considered Related to the Study Drug

	Lorvotuzumab Mertansine Dose Level (mg/m^2), n (%)						
Adverse Event	**40 (N = 3)**	**60 (N = 3)**	**75 (N = 3)**	**90 (N = 3)**	**112 (N = 19)**	**140 (N = 6)**	**Overall (N = 37)**
Fatigue	0	0	0	0	0	2 (33.3)	2 (5.4)
Areflexia	0	0	0	0	1 (5.3)	0	1 (2.7)
Asthenia	0	0	0	0	1 (5.3)	0	1 (2.7)
Hyperuricemia	0	0	0	1 (33.3)	0	0	1 (2.7)
Increased lipase	0	0	0	0	1 (5.3)	0	1 (2.7)
Myalgia	0	0	0	0	0	1 (16.7)	1 (2.7)
Peripheral neuropathy	0	0	0	0	1 (5.3)	0	1 (2.7)
Neutropenia	0	0	0	0	1 (5.3)	0	1 (2.7)
Kidney dysfunction	0	0	0	0	0	1 (16.7)	1 (2.7)

Table 3

Best Response to Therapy by Study Cohort and Overall, in Patients Evaluable for Response (n = 35)

	Lorvotuzumab Mertansine Dose Level (mg/m^2), n (%)						
Best Tumor Response	**40 (N = 3)**	**60 (N = 3)**	**75 (N = 3)**	**90 (N = 3)**	**112 (N = 19)**	**140 (N = 6)**	**Overall (N = 37)**
Evaluable patients	3	3	3	3	17	6	35
CR	0	0	0	0	0	0	0
PR	0	0	0	0	1 (5.9)	1 (16.7)	2 (5.7)
MR	0	1 (33.3)	0	1 (33.3)	2 (11.8)	0	4 (11.4)
NC	0	2 (66.7)	1 (33.3)	1 (33.3)	6 (35.3)	5 (83.3)	15 (42.9)
PD	3 (100)	0	2 (66.7)	1 (33.3)	8 (47.1)	0	14 (40.0)

Abbreviations: CR = complete response; MR = minor response; NC = no change; PD = progressive disease; PR = partial response.

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