Zilovertamab Vedotin Targeting of ROR1 as Therapy for Lymphoid Cancers


Abstract

BACKGROUND Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an oncofetal protein present on many cancers. Zilovertamab vedotin (ZV) is an antibody–drug conjugate comprising a monoclonal antibody recognizing extracellular ROR1, a cleavable linker, and the anti-microtubule cytotoxin monomethyl auristatin E.

METHODS In this phase 1, first-in-human, dose-escalation study, we accrued patients with previously treated lymphoid cancers to receive ZV every 3 weeks until the occurrence of cancer progression or unacceptable toxicity had occurred.

RESULTS We enrolled 32 patients with tumor histologies of mantle cell lymphoma (MCL) (n=15), chronic lymphocytic leukemia (n=7), diffuse large B-cell lymphoma (DLBCL) (n=5), follicular lymphoma (n=3), Richter transformation lymphoma (n=1), or marginal zone lymphoma (n=1). Patients had received a median of four previous drug and/or cellular therapies. Starting dose levels were 0.5 (n=1), 1.0 (n=3), 1.5 (n=3), 2.25 (n=11), and 2.5 (n=14) mg per kg of body weight (mg/kg). Pharmacokinetic and pharmacodynamic data documented systemic ZV exposure and exposure-dependent ZV targeting of ROR1 on circulating tumor cells. As expected with an monomethyl auristatin E-containing antibody–drug conjugate, adverse events (AEs) included acute neutropenia and cumulative neuropathy resulting in a recommended ZV dosing regimen of 2.5 mg/kg every 3 weeks. No clinically concerning AEs occurred to suggest ROR1-mediated toxicities or nonspecific ZV binding to normal tissues. ZV induced objective tumor responses in 7 of 15 patients with MCL (47%; 4 partial and 3 complete) and in 3 of 5 patients with DLBCL (60%; 1 partial and 2 complete); objective tumor responses were not observed among patients with other tumor types.

CONCLUSIONS In heavily pretreated patients, ZV demonstrated no unexpected toxicities and showed evidence of antitumor activity, providing clinical proof of concept for selective targeting of ROR1 as a potential new approach to cancer therapy. (ClinicalTrials.gov number, NCT03833180.)
Background

Lymphoid cancers arise from monoclonal neoplastic lymphocytes, which can accumulate in lymph nodes, blood, bone marrow, spleen, and liver. These disorders can cause constitutional symptoms, lymphadenopathy, organomegaly, myelosuppression, and immunocompromise.\(^1\)\(^-\)\(^3\) Although chemoimmunotherapeutic regimens often provide durable remission,\(^4\) many patients have disease relapse and ultimately die as a result of their cancers.\(^5\)\(^-\)\(^10\) New mechanisms of action are needed to safely offer new treatments for patients with lymphoid malignancies that have become resistant to existing therapies.

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a cell-surface protein that mediates signaling from its ligand, Wnt5a, to drive physiologic embryonic stem cell proliferation.\(^11\)\(^-\)\(^13\) By birth, ROR1 expression disappears from almost all normal tissues. However, cancer cells that revert to a dedifferentiated state can express ROR1.\(^14\)\(^,\)\(^15\) ROR1-expressing hematologic and solid tumors have a high potential for self-renewal, exhibit increased survival and migration, and are associated with poor outcomes.\(^15\)\(^-\)\(^20\)

Zilovertamab vedotin (ZV; previously VLS-101) is a novel antibody-drug conjugate comprising the humanized monoclonal antibody zilovertamab (previously UC-961 or cirmtuzumab), which is highly specific for tumor tissue;\(^21\)\(^,\)\(^22\); a proteolytically cleavable maleimido-caproyl-valine-citrulline-para-aminobenzoate linker; and the antitubulose cytokotoxin monomethyl auristatin E (linker-monomethyl auristatin E designated as vedotin). ZV binding to tumor cell ROR1 results in rapid internalization, trafficking to lysosomes, antibody-drug conjugate cleavage, and monomethyl auristatin E release. In mouse models of human lymphoid cancers, ZV safely induced tumor shrinkage, often causing complete regressions even with heterogenous ROR1 expression.\(^23\)\(^-\)\(^25\) Dose-dependent neutropenia was the only toxicologically meaningful adverse effect in monkeys. Here, we report the results of a clinical study successfully targeting ROR1 with an antibody-drug conjugate.

Methods

STUDY DESIGN AND CONDUCT

We conducted a phase 1, first-in-human, sequential ascending-dose trial evaluating the safety, immunogenicity, pharmacokinetics, pharmacodynamics, and efficacy of ZV in patients with previously treated lymphoid cancers. The study was sponsored and funded by VelosBio Inc. (San Diego, CA), now a wholly owned subsidiary of Merck & Co., Inc. (Kenilworth, NJ). The protocol was approved by institutional review boards for each center, and patients gave written informed consent before study participation. The study was overseen by the Food and Drug Administration (FDA).

The study was designed and conducted through close cooperation among authors representing the sponsor, collaborating organizations, and investigational sites. The authors were responsible for aspects of study design pertinent to their expertise: medical and regulatory oversite, enrollment of study participants, collation of the data, and analyses of clinical, pharmacodynamic, and pharmacokinetic findings. All the authors were engaged in manuscript preparation and confirm adherence to the protocol, the completeness and accuracy of the results, and the collective decision to publish the paper. Only those listed as authors contributed to manuscript preparation.

STUDY PATIENTS

Study patients were adults with adequate performance status and organ function who had a lymphoid cancer that had progressed after appropriate prior therapy and were not candidates for high-dose therapy with hematopoietic stem cell transplantation (HDT/HSCT) or chimeric antigen receptor (CAR)-T-cell therapy. Patients with conditions or medication usage that might compromise safety or confound results were excluded. Because ROR1 is commonly expressed on hematological cancers\(^14\)\(^,\)\(^16\)\(^-\)\(^18\) and a validated ROR1 expression assay remains in development, we did not preselect patients for ROR1 expression.

STUDY DRUG ADMINISTRATION AND SUPPORTIVE CARE

ZV was manufactured at WuXi Biologics (Wuxi, China). The drug was supplied as a frozen liquid containing 50 mg of ZV in 5 ml of formulation buffer (10 mg/ml). After dilution in 5% dextrose in water, ZV was administered intravenously for 30 minutes every 3 weeks until cancer progression or unacceptable toxicity had occurred. This dosing schedule was considered appropriate given the pattern of neutropenia observed after VLS-101 administration in monkeys and clinical experience with other monomethyl auristatin E-containing antibody-drug conjugates.\(^26\)\(^,\)\(^27\) We enrolled one patient at the ZV starting-dose...
level of 0.5 mg per kilogram of body weight; this initial dose level represented the allometrically scaled human equivalent dose as derived from monkey toxicology studies adjusted by a safety factor of approximately 6. Successive patient cohorts were enrolled at ZV starting doses of 1.0, 1.5, 2.25, and 2.5 mg per kg body weight (mg/kg) using a 3 + 3 dose escalation based on evaluation of dose-limiting toxicities in cycle 1. Per protocol, we truncated the dose escalation and expanded the 2.25 and 2.5 mg/kg starting-dose-level cohorts considering the emerging ZV safety profile and an FDA proscription against evaluation of ZV doses higher than 2.5 mg/kg based on FDA experience with other monomethyl auristatin E-containing antibody-drug conjugates. We used upward or downward dose modification to achieve the highest individually tolerated ZV dose up to 2.5 mg/kg.

We provided initial tumor lysis syndrome prophylaxis based on tumor lysis syndrome risk but did not routinely administer infusion-reaction or antiemetic prophylaxis. We permitted granulocyte colony-stimulating factor for prevention of neutropenia.

STUDY ASSESSMENTS

We coded adverse events (AEs) using the Medical Dictionary for Regulatory Activities and graded AEs using the Common Terminology Criteria for Adverse Events, Version 5.0. A central cardiology laboratory (ERT, etc.) reviewed electrocardiography data. In patients with circulating tumor cells, we used flow cytometry to assess ROR1 occupancy. We employed noncompartmental methods to derive plasma antibody-drug conjugate and monomethyl auristatin E pharmacokinetic parameters from validated bioanalytic assays and assessed for serum antibody-drug conjugate and drug antibodies using a validated immunoassay (PPD Laboratories, Richmond, VA). We evaluated efficacy with standard criteria at a central radiographic imaging facility (Bioclinica, Princeton, NJ). Given the phase 1, dose-ranging study design, there was no preestablished statistical hypothesis, and all analyses were descriptive.

Results

PATIENT DISPOSITION AND CHARACTERISTICS

Between March 2019 and April 2020, we enrolled 32 patients. The data collection cutoff was November 27, 2020. Study therapy was discontinued in 30 patients (22 for cancer progression or inadequate benefit and 8 for AEs), and 2 patients continued to receive therapy (Table S-1 in the Supplementary Appendix, available at evidence.nejm.org).

Table 1 summarizes baseline patient characteristics. Consistent with the epidemiology of adult lymphoid cancers, the median age was 70 years and the patients were predominantly male, consistent with other studies of adult lymphoid cancers. Eastern Cooperative Oncology Group performance status was 0 or 1 (on a 5-point scale, with 0 indicating no symptoms and higher scores indicating increasing disability) in 87.5% of patients.

The most frequent diagnoses were mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and diffuse large B-cell lymphoma (DLBCL). Most patients (59.4%) were categorized as being at intermediate or high risk for tumor lysis syndrome on the basis of elevated serum lactate dehydrogenase, bulky adenopathy, circulating malignant lymphocytes, or a combination of these factors. The majority of patients with MCL (13 of 15; 87%) had intermediate- or high-risk Mantle Cell Lymphoma International Prognostic Index scores (Table S-2).

Patients had received a median of four prior systemic therapies (Table 1). All patients had received prior anti-CD20 antibodies (Table S-3), and all 15 patients with MCL had received a Bruton’s tyrosine kinase inhibitor (BTKi), including 13 who had discontinued the BTKi for progressive disease and 2 who had discontinued after more than 1 year for atrial fibrillation. Five patients (four with MCL and one with DLBCL) had undergone HDT autologous HSCT, six (four with DLBCL, one with Richter transformation lymphoma [RTL], and one with CLL) had received CAR-T cells, and one (with RTL) had received CAR-natural killer cells.

DOSE ESCALATION AND STUDY DRUG ADMINISTRATION

Across the five ZV starting-dose levels (0.5, 1.0, 1.5, 2.25, and 2.5 mg/kg), we administered 174 infusions using the every-3-week schedule (Table S-5). The number of cycles of therapy ranged from 1 to 16.

We did not observe first-cycle dose-limiting toxicities at ZV starting-dose levels of 0.5 (n=1), 1.0 (n=3), or 1.5 (n=3) mg/kg. We observed grade 4 neutropenia in 1 of 10 dose-limiting toxicity-evaluable patients who received...
Zilovertamab vedotin. Source: The authors.

Hematopoietic stem cell transplantation, LDH lactate dehydrogenase, NK natural killer (cell), tumor lysis syndrome, ULN upper limit of normal.

ALC denotes absolute lymphocyte count, CAR chimeric antigen receptor, ECOG Eastern Cooperative Oncology Group, HDT/HSCT high-dose therapy with hematopoietic stem cell transplantation, LDH lactate dehydrogenase, NK natural killer (cell), tumor lysis syndrome, ULN upper limit of normal, and ZV zilvertamab vedotin.

For patients enrolled at lower starting-dose levels, we increased subsequent ZV doses to the highest tolerable doses up to 2.5 mg/kg. Consequently, we administered most ZV infusions at 2.25 (58 infusions) or 2.5 mg/kg (57 infusions) (Table S-5). Some patients receiving these higher dose levels required dose modification; we instituted 21 ZV dose delays or reductions in 12 patients; the majority were caused by peripheral neuropathy (9 times among 6 patients) or neutropenia (5 times in 3 patients) (Table S-8). The eight discontinuations for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ZV Starting Dose Level, Every 3 Wk</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.5 mg/kg (N=1)</td>
</tr>
<tr>
<td>Age Median (range) — years</td>
<td>59</td>
</tr>
<tr>
<td>&lt;65 years — no. (%)</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>≥65 years — no. (%)</td>
<td>0</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>ECOG performance status — no. (%)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cancer diagnosis — no. (%)</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Richter transformation lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Baseline tumor lysis syndrome category — no. (%)†</td>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>Median — no. (range)‡</td>
</tr>
<tr>
<td>HDT/HSCT — no. (%)</td>
<td>0</td>
</tr>
<tr>
<td>CAR–T-cell therapy — no. (%)</td>
<td>1 (100.0)</td>
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<tr>
<td>CAR–NK-cell therapy — no. (%)</td>
<td>0</td>
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</table>

*Protocol tumor lysis syndrome categories were as follows: low risk, which was serum LDH at or lower than ULN, all measurable lymph nodes <5-cm diameter, and ALC <25 x 10⁹/l; intermediate risk, which was serum LDH >1 to <2 times ULN, ≥1 measurable lymph node of ≥5- but <10-cm diameter, or ALC ≥25 x 10⁹/l; and high risk, which was serum LDH ≥2 times ULN, ≥1 measurable lymph node of ≥10-cm diameter, or both ≥1 measurable lymph nodes with ≥5- but <10-cm diameter and ALC ≥25 x 10⁹/l.†This included conditioning regimens administered in association with HDT/HSCT, CAR-T cells, or CAR-NK cells.

ALC denotes absolute lymphocyte count, CAR chimeric antigen receptor, ECOG Eastern Cooperative Oncology Group, HDT/HSCT high-dose therapy with hematopoietic stem cell transplantation, LDH lactate dehydrogenase, NK natural killer (cell), tumor lysis syndrome, ULN upper limit of normal, and ZV zilvertamab vedotin. Source: The authors.

2.25 mg/kg (10.0%); this patient continued at 1.5 mg/kg in cycle 2 before reescalation to 2.25 and 2.5 mg/kg with pegfilgrastim. We observed first-cycle dose-limiting toxicities in 3 of 14 patients who received 2.5 mg/kg (21.4%), comprising grade 4 neutropenia resulting in a ZV reduction to 2.25 mg/kg in cycle 2 (n=1), grade 3 febrile neutropenia during disease-related liver failure that resulted in ZV discontinuation after cycle 1 (n=1), and grade 3 diarrhea resulting in a ZV reduction to 1.5 mg/kg in cycle 2 (n=1).
AEs were primarily for cumulative neuropathy (Tables S-1 and S-9).

PHARMACOKINETICS
Pharmacokinetic data documented systemic ZV exposure (Fig. S-1 and Table S-6). Plasma antibody-drug conjugate concentrations peaked shortly after the infusion, while monomethyl auristatin E concentrations peaked approximately 3 days after the infusion, consistent with slow release of the cytotoxin at substantially lower levels than the antibody-drug conjugate. Plasma antibody-drug conjugate and monomethyl auristatin E exposures generally rose proportionally with dose. The median antibody-drug conjugate half-life was 3.8 days across all dose levels.

PHARMACODYNAMICS
We documented ZV binding to cancer cell RORI in three patients (two with CLL and one with MCL) who had circulating tumor cells. ZV bound rapidly to RORI; only 22.7%, 12.8%, and 8.2% of RORI was unoccupied by ZV at the end of the infusion at doses of 1.0, 2.25, and 2.5 mg/kg, respectively (Fig. 1A). The proportion of receptors unoccupied by ZV rose by day 8 at a dose of 1.0 mg/kg and by day 15 at a dose of 2.25 or 2.5 mg/kg. Loss of RORI occupancy by ZV corresponded to simultaneous decreases in ZV plasma concentrations (Fig. 1B).

SAFETY
AEs occurring in five or more patients are listed in Table S-7, and AEs of grade 3 or higher severity occurring in three or more patients are described in Table 2.

Sites reported grade 3 or higher decreases in neutrophils, hemoglobin, and platelets as AEs (Table 2) and as laboratory abnormalities (Table S-11). Neutropenia appeared to be dose related in frequency and severity. Decreased hemoglobin and platelet counts occurred in the setting of preexisting cancer-related bone marrow compromise, and a drug effect was not obvious.

We documented baseline neuropathy in 12 of 32 patients (37.5%), consistent with prior use of neuropathy-inducing chemotherapy in 19 of 32 patients (59.4%) (Table S-4). Treatment-emergent neuropathy occurred in 14 of 32 patients (43.8%) (Table S-7), with maximum intensities being grade 1 in 3 of 32 (9.4%), grade 2 in 7 of 32 (21.9%), and grade 3 in 4 of 32 (12.5%). Respective median times to grade 1 or higher, grade 2 or higher, and grade 3 neuropathy were 15.6, 23.1, and 39.1 weeks, respectively, whereas median time from first grade 2 or higher neuropathy to grade 1 or lower resolution was 21.3 weeks (Fig. S-2).

Nausea and vomiting events at any time during the study were reported in 19 of 32 patients (59.4%) and 9 of 32 patients (28.1%), respectively. We did not routinely administer antiemetic prophylaxis and, considering nausea or vomiting on or within 1 day after drug administration, such events were infrequent, being described following 8 of 174 infusions (4.6%) and 1 of 174 infusions (0.6%), respectively. We observed diarrhea at any time during the study in 13 of 32 patients (40.6%); 3 of 32 patients (9.4%) had grade 3 events; diarrhea attributions included ZV, infection, or other drugs. We saw nonneutropenic pneumonia in 4 of 32 patients (12.5%) (grade 2 in 1 patient and grade 3 in 3 patients) (Table S-7). All 4 of these patients recovered with antibiotic therapy; 3 resumed ZV, while 1 discontinued the study drug given a lack of improvement in the patient’s CLL. We noted low-grade stomatitis in 6 of 32 patients (18.8%). Alopecia occurred in 5 of 32 subjects (15.6%). We observed 28 serious AE (SAE) terms in 18 SAE cases involving 11 subjects (Table S-10). No patients died within 30 days of the last ZV dose.

Biochemistry abnormalities were typically low grade (Table S-12). Grade 3 or higher serum glucose elevations occurred in patients with diabetes or administered glucocorticoids, and no drug-dependent pattern was evident. Other grade 3 to 4 biochemistry elevations were incidental, asymptomatic, and nonpersistent.

We did not observe drug-related electrocardiographic changes. Fridericia-corrected cardiac QT interval (QTcF) prolongations occurred in 6 of 32 patients (18.8%); these appeared to be random fluctuations and did not correlate with ZV dose or plasma antibody-drug conjugate or monomethyl auristatin E concentrations (Table S-13).

We did not find clinically relevant immunogenicity; low-titer antidrug antibodies in one patient (3.1%) (Table S-14) did not adversely affect pharmacokinetics or efficacy (data not shown).

EFFICACY
Among patients with CLL (n=7), follicular lymphoma (n=3), RTL (n=1), or marginal zone lymphoma (n=1), we did not see antitumor activity. However, in patients with MCL (n=15) and DLBCL (n=5), we observed objective tumor responses.

Figure 2A displays the best changes in index tumor dimensions during therapy. We documented objective responses
Figure 1. ROR1 Occupancy, Total Antibody-Drug Conjugate, and Monomethyl Auristatin E Plasma Concentrations in Patients with CLL or MCL.

(A) CLL or MCL cells were isolated with cell-surface markers CD5 and CD19, and available ROR1 receptors were quantified with PE-conjugated zilovertamab. As patients were treated with ZV, zilovertamab-PE was displaced from ROR1 by ZV, permitting determination of the proportion of receptors unoccupied by ZV relative to the predose baseline (C1D1). (B) Total antibody-drug conjugate and monomethyl auristatin E plasma concentrations were measured with validated bioanalytic assays. ADC denotes antibody–drug conjugate, CLL chronic lymphocytic leukemia, CxDy cycle x day y, LLQ lower limit of quantification, MCL mantle cell lymphoma, MMAE monomethyl auristatin E, PE phycoerythrin, ROR1 receptor tyrosine kinase-like orphan receptor 1, and ZV zilovertamab vedotin.
**Discussion**

This study derives from research to characterize RORI and to develop zilovertamab as a RORI-specific antibody with nonclinical and clinical safety when administered in its unconjugated form. For development of the antibody-drug conjugate, we chose to conjugate zilovertamab with vedotin as the linker-cytotoxin, knowing that vedotin’s well-characterized safety profile would allow us to assess the selectivity of ZV. We focused on lymphoid cancers given their near-ubiquitous RORI expression and their known responsiveness to non-cancer-specific, lymphocyte-targeting drugs such as brentuximab vedotin and polatuzumab vedotin that deliver monomethyl auristatin E.

ZV plasma pharmacokinetics were generally consistent with those of other monomethyl auristatin E-containing antibody-drug conjugates. Pharmacodynamic data confirmed exposure-dependent ZV targeting of RORI.

We obtained safety results in older, heavily pretreated patients representative of those likely to receive ZV in future clinical trials. As expected with an monomethyl auristatin E-containing antibody-drug conjugate, we observed neutropenia as an acute, dose-dependent AE; secondary prophylaxis with long-acting G-CSF appeared able to minimize neutropenia and maximize on-time drug delivery. As was also expected on the basis of experience with other monomethyl auristatin E-containing antibody-drug conjugates, we observed monomethyl auristatin E-mediated neuropathy as a cumulative AE. Incidence, severity, time to onset, and discontinuations due to neuropathy with ZV appeared consistent with findings with

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### Table 2. Grade 3 or Higher Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>ZV Starting Dose Level, Every 3 Wk</th>
<th>Total mg/kg (N=32)</th>
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<tbody>
<tr>
<td></td>
<td>0.5 mg/kg (N=1)</td>
<td></td>
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<tr>
<td></td>
<td>1.0 mg/kg (N=3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 mg/kg (N=3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.25 mg/kg (N=11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg (N=14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any patient with grade ≥3 TEAE</td>
<td>0 (2 [66.7])</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Investigations</td>
<td>0 (2 [66.7])</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0 (1 [33.3])</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>0 (1 [33.3])</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>0 (1 [33.3])</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0 (1 [33.3])</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*All events were grade 3, with the following exceptions: grade 4 neutrophil count decreased in three patients receiving 2.25 mg/kg Q1/3W and in two patients receiving 2.5 mg/kg Q1/3W, grade 4 platelet count decreased in three patients receiving 2.5 mg/kg Q1/3W, and grade 4 white blood cell count decreased in one patient receiving 2.5 mg/kg Q1/3W.

†This includes any of the following terms: peripheral sensory neuropathy, peripheral motor neuropathy, neuropathy peripheral, hypoesthesia (numbness), paresthesia (tingling), and/or neuralgia (neuropathic pain).

This table includes grade ≥3 adverse events that were treatment emergent (i.e., that occurred or worsened in the period from the first dose of study drug to 30 days after the last dose of study drug) and that occurred in three or more patients. A patient reporting the same TEAE of grade ≥3 or higher was counted only once. MedDRA denotes Medical Dictionary for Regulatory Activities, TEAE treatment-emergent adverse event, and ZV zilovertamab vedotin. Source: The authors.

(five partial and two complete) in 7 of 15 patients with MCL (46.7%). Two additional patients with MCL experienced more than 50% tumor regressions by site assessments but were designated as having stable disease because the lesions were considered nonindex on independent review. One additional patient had an 80% decrease in systemic disease but developed central nervous system MCL. We documented objective tumor responses (one partial and two complete) in three of five patients with DLBCL (60%).

**Figure 2B** displays changes over time in index tumor dimensions. From therapy start, responses extended to 17, 19, 47+, 49, 54+, 61, and 67+ weeks in responding patients with MCL and 28, 44+, and 60+ weeks in responding patients with DLBCL.
Figure 2. Overall Response Assessments, Best Changes in Tumor Dimensions, and Time Course of Changes in Tumor Dimensions.

*a* Change in tumor dimensions is set to ≥50% in three patients (009-0003, 001-0002, and 001-0012) with clinical PD and no postbaseline scan and one patient (003-0001) with no index disease on independent review who developed new lesions at 8.6 weeks that grew further by 18.3 weeks.

*b* Patient 010-0002 with splenic and peripheral blood MCL had a 59% decrease in excess spleen size (displayed on graph) and an 89% decrease in ALC (blood mantle cells) from 27.9 × 10^9/l to 3.1 × 10^9/l (WNL) by cycle 1 day 15.

*c* Patient 001-0003 with MCL was considered to have only nonindex disease on independent review; site tumor response dimensions are shown based on investigational site radiographic measurements supported by physical examination and symptomatic improvements.

*d* Patient 005-0006 with MCL had an 80% decrease in systemic index disease but developed new central nervous system MCL.

*e* On independent review, Patient 002-0001 with DLBCL had a 100% decrease in index disease by CT and SD by PET.

All tumor assessments available as of November 27, 2020 are included. Tumor dimensions and best overall response determinations are based on independent review unless noted. The dotted lines indicate the minimum threshold for an objective response. Patients with MCL responses had 2, 3, 4, 5, and 8 prior regimens (including HDT/HSCT in 2 patients). Patients with DLBCL responses had 3, 7, and 7 prior regimens (including HDT/HSCT in 1 patient and CAR–T cells in 3 patients). ALC denotes absolute lymphocyte count, CAR-T chimeric antigen receptor–T cell, CLL chronic lymphocytic leukemia, CR complete response, CT computed tomography, DLBCL diffuse large B-cell lymphoma, FL follicular lymphoma, HDI/HSCT high-dose therapy with hematopoietic stem cell transplantation, MCL mantle cell lymphoma, MZL marginal zone lymphoma, OR objective response, ORR overall response rate, PD progressive disease, PET positron emission tomography, PR partial response, RTL Richter transformation lymphoma, SD stable disease, SPD sum of the products of the perpendicular diameters, WNL within normal limits, and ZV zilovertam vedotin.
other monomethyl auristatin E-containing antibody-drug conjugates (Table S-15). We managed neuropathy with ZV interruptions, modifications, or discontinuations and saw neuropathy recover to grade 1 or lower in patients for whom follow-up was available. Diarrhea occurred at rates generally comparable to those observed with other monomethyl auristatin E-containing antibody-drug conjugates\(^\text{34,35}\) and was considered related to ZV in some patients. We managed diarrhea with evaluation for alternative causes, antidiarrheals, and/or dose modification. We infrequently observed stomatitis and alopecia.

We found no clinical evidence of non-monomethyl auristatin E-related AEs that would suggest ROR1-mediated AEs or widespread nonspecific binding to normal tissues. We consistently infused ZV over 30 minutes without acute AEs. Specifically, ZV did not provoke tumor lysis syndrome or infusion reactions, and rates of acute, treatment-related nausea or vomiting were low. Thus, routine prophylaxis against such AEs is not required with ZV monotherapy. As for other monomethyl auristatin E-containing antibody-drug conjugates\(^\text{34,35}\) we did not see drug-related QT prolongation. We saw no clinically concerning ocular, cardiovascular, hepatic, renal, metabolic, or cutaneous AEs. Other investigators have detected ROR1 in parathyroid gland and pancreatic islet cells using an antibody to an intracellular epitope.\(^\text{39}\) However, zilovertamab recognizes an extracellular ROR1 epitope, and we saw no progressive ZV-related perturbations of calcium or glucose metabolism suggesting parathyroid or islet cell dysfunction. We did not observe clinically consequential ZV immunogenicity.

Considering cycle 1 dose-limiting toxicity data, ZV dose escalations in subsequent cycles, dose modifications for neutropenia, G-CSF prophylaxis in later cycles, and cumulative neuropathy, 2.5 mg/kg was considered the recommended phase 2 starting dose when administering ZV every 3 weeks. This ZV dose appears consistent with starting doses of 2.3 or 2.4 mg/kg for multiple monomethyl auristatin E-containing antibody-drug conjugates evaluated by FDA reviewers.\(^\text{40}\)

In this small, first-in-human safety trial of ZV, we also observed therapeutic efficacy in some of our patients. ZV induced regressions in several patients with MCL and DLBCL who had received extensive prior therapy, including BTKi for MCL and HDT/HSCT and/or CAR-T cells. Tumor responses were transient in some patients but were longer in others (i.e., extending to 10 or more months at the time of the data cutoff date in 7 of 10 patients with responding tumors). These results are encouraging given poor outcomes after failure of BTKi for MCL\(^\text{5-8}\) or CAR-T-cell therapy for DLBCL.\(^\text{10}\) We did not observe objective responses among seven patients with CLL despite known high-frequency ROR1 expression in this cancer. Polatuzumab vedotin also lacked efficacy in patients with CLL\(^\text{27}\) suggesting a disease-specific lack of responsiveness to monomethyl auristatin E. ZV efficacy in larger numbers of patients with other ROR1-expressing lymphoid cancers requires exploration.

The correlation of ROR1 expression with efficacy is unknown. Given that clinical biomarker assays for tumor ROR1 expression remain in development, we passively enriched our study population for ROR1-expressing tumors. ROR1 is labile in archival paraffin-embedded tissue,\(^\text{32}\) and candidate assays require validation in phase 2 testing to assess sensitivity and predictive potential by tumor type, frequency of ROR1 expression, and cytotoxin sensitivity.

Our findings provide clinical equipoise to support the further development of ZV as monotherapy and combination therapy in patients with monomethyl auristatin E-sensitive hematological and solid tumors. Importantly, our data provide validation of ROR1 as a therapeutic target, supporting the concept that selective targeting of ROR1 may offer a novel and clinically beneficial approach to cancer therapy if these data can be extended in larger and longer clinical trials.

**Disclosures**

Disclosure forms provided by the authors are available with the full text of this article at [evidence.nejm.org](http://evidence.nejm.org).

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