Original Study

Phase 1/2 Study of the CD56-Targeting Antibody-Drug Conjugate Lorvotuzumab Mertansine (IMGN901) in Combination With Carboplatin/Etoposide in Small-Cell Lung Cancer Patients With Extensive-Stage Disease

Mark A. Socinski,[1] Frederic J. Kaye,[2] David R. Spigel,[3] Fred J. Kudrik,[4] Santiago Ponce,[5] Peter M. Ellis,[6] Margarita Majem,[7] Paul Lorigan,[8] Leena Gandhi,[9] Martin E. Gutierrez,[10] Dale Nepert,[11] Jesus Corral,[5] Luis Paz Ares[5]

Abstract

Lorvotuzumab mertansine (LM, IMGN901) is a CD56-targeting antibody-drug conjugate developed for tumor-selective delivery of the cytotoxic maytansinoid DM1. This phase 1/2 study evaluated the combination of LM with first-line carboplatin/etoposide chemotherapy in patients with extensive-disease small-cell lung cancer. Overall, modest improvements in patient tumor responses did not outweigh the increased safety risks of the triplet combination.

Introduction: This trial assessed the safety and efficacy of LM in combination with carboplatin/etoposide therapy compared to carboplatin/etoposide treatment alone in patients with previously untreated extensive-disease small-cell lung cancer (ED-SCLC). **Patients and Methods:** A run-in phase 1 stage was used to determine the recommended phase 2 dose and characterize the dose-limiting toxicities of LM in combination with carboplatin/etoposide followed by LM alone in patients with CD56-positive solid tumors. In phase 2, chemotherapy-naive ED-SCLC patients were randomized 2:1 to carboplatin AUC (area under the plasma concentration vs. time curve) of 5 day 1 + etoposide 100 mg/m^2 days 1 to 3 plus LM (arm 1) or alone (arm 2). **Results:** In the phase 1 study (n = 33), a dose of LM at 112 mg/m^2 with carboplatin/etoposide was identified as the recommended phase 2 dose. However, because of an increased incidence of peripheral neuropathy events during early phase 2, this dose was reduced to 90 mg/m^2. In phase 2, a total of 94 and 47 evaluable patients were assigned to arms 1 and 2, respectively. No difference in median progression-free survival was observed between arms 1 and 2 (6.2 vs. 6.7 months). The most common treatment-emergent adverse event leading to discontinuation was peripheral neuropathy (29%). A total of 21 patients had a treatment-emergent adverse event leading to death (18 in arm 1 and 3 in arm 2); for 10 individuals, this was an infection (pneumonia or sepsis) deemed to be related to the study drug. **Conclusion:** The combination of LM plus carboplatin/etoposide did not improve efficacy over standard carboplatin/etoposide doublet therapy in ED-SCLC patients and showed increased toxicity, including a higher incidence of serious infections with fatal outcomes.

Clinical Lung Cancer, Vol. 18, No. 1, 68-76 © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Clinical trial, Combination therapy, SCLC, Targeted drug delivery, Tolerability

[1]Division of Hematology/Oncology, Univeristy of Pittsburgh Cancer Institute, Pittsburgh, PA
[2]Hematology-Oncology, University of Florida College of Medicine, Gainesville, FL
[3]Lung Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN
[4]Cancer Center, South Carolina Oncology Associates, Columbia, SC
[5]Medical Oncology Department, Hospital Universitario 12 de Octubre and Lung Cancer Unit CNIO, Madrid, Spain
[6]Medical Oncology, Juravinski Cancer Centre, Hamilton, Ontario, Canada
[7]Servei d'Oncologia Mèdica, Hospital Sant Pau, Barcelona, Spain
[8]Division of Molecular and Clinical Cancer Sciences, University of Manchester/Christie NHS Foundation Trust, Manchester, UK
[9]Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, Boston, MA
[10]Bienes Cancer Center, Holy Cross Hospital, Fort Lauderdale, FL
[11]Clinical Development, ImmunoGen Inc, Waltham, MA

Submitted: Jun 20, 2016; Revised: Aug 31, 2016; Accepted: Sep 6, 2016; Epub: Oct 3, 2016

Address for correspondence: Mark A. Socinski, MD, Division of Hematology/Oncology, University of Pittsburgh, 5150 Center Ave, Pittsburgh, PA 15232
Fax: (412) 648-6579; e-mail contact: socinskima@upmc.edu

1525-7304/© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.cllc.2016.09.002

Introduction

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine tumor that accounts for approximately 15% of all lung cancer cases.[1] SCLC has a high propensity to metastasize early during disease development. At diagnosis, it is classified into either limited-stage disease (LD) or extensive-stage disease (ED). LD-SCLC is characterized by tumor confinement, generally to one hemithorax and encompassable in a single radiation field. A majority of patients (~70%), however, present with extensive-disease small-cell lung cancer (ED-SCLC), showing dissemination beyond this region, most commonly to the contralateral lung, liver, brain, and bones.[2]

Treatment strategies for SCLC have changed little over recent decades,[3] with concurrent chemoradiation or chemotherapy alone providing the foundations for LD-SCLC and ED-SCLC standard of care, respectively.[4] Thoracic radiotherapy, preferably administered early during the initial cycles of chemotherapy, plays an indispensable role in the treatment of LD-SCLC.[4] The ability of radiotherapy to improve outcomes for individuals with ED-SCLC, however, either in the consolidative or prophylactic settings, is less well established.[5] Thus, etoposide in combination with a platinum agent (carboplatin or cisplatin) remains the standard first-line option for ED-SCLC patients.[6] Despite a high likelihood of initial response to therapy, most patients eventually experience relapse with resistant disease. Median overall survival (OS) times of only 8 to 11 months are achieved with standard therapies.[7] In an effort to improve outcomes in ED-SCLC, a number of alternative approaches have been evaluated, such as 3-drug combinations, sequential combination therapies, and dose-intensified schedules.[8-10] To date, none of these alternate modalities has demonstrated a significant survival advantage over current combination therapy; the development of new strategies to effectively combat SCLC thus represents a critical unmet medical need.

Lorvotuzumab mertansine (LM, IMGN901) is an antibody-drug conjugate comprising a humanized anti-CD56 monoclonal antibody (huN901, lorvotuzumab) covalently coupled, via disulfide linkage, to the cytotoxic maytansinoid DM1.[11] CD56, also known as NCAM1, is a member of the neural cell adhesion molecule family[12] that is primarily expressed on natural killer cells and T-cell lineages.[13] Aberrant CD56 expression is also observed in a variety of human cancers, and for solid tumors, it serves as a diagnostic biomarker to identify those of neuroendocrine origin, including SCLC.[14-16] LM binds with high affinity and specificity to CD56 on the surface of tumor cells, resulting in internalization of the antibody-drug conjugate and subsequent intracellular release of DM1 due to cleavage of its disulfide bond with the linker.[17] This in turn promotes disruption of microtubule assembly, G2/metaphase arrest, and ultimately apoptosis.[18-20] In preclinical studies, LM has shown robust antitumor activity in CD56-positive tumors, most notably in models of SCLC.[21] Further, preliminary signs of efficacy have been observed in SCLC patients undergoing LM monotherapy as part of a phase 1 study in patients with CD56-positive solid tumors.[22]

Here we report the findings of an open-label, multicenter phase 1/2 study designed to assess the safety and efficacy of LM when administered in combination with carboplatin/etoposide doublet therapy. The dose-finding phase 1 component was a lead-in to a randomized phase 2 design comparing LM combination therapy to carboplatin/etoposide treatment alone in ED-SCLC patients.

Patients and Methods

Patients

For the phase 1 portion of the trial, patients with advanced solid tumors for whom treatment with carboplatin/etoposide was a reasonable therapeutic option were eligible to participate. Only patients with histologically or cytologically confirmed ED-SCLC and who were chemotherapy naive were enrolled onto the phase 2 portion of the study. All patients had to be $\geq$ 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (phase 1) or $\leq$ 2 (phase 2), and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) (phase 2). Adequate hematologic and organ function were also required. Key exclusion criteria included known hypersensitivity to monoclonal antibody therapy, maytansinoids, or etoposide; a history of allergic reaction to platinum-containing compounds; $>$ 3 prior cytotoxic regimens (phase 1 only); or a previous malignancy with $<$ 3-year disease-free interval other than basal-cell or squamous-cell carcinoma, or in-situ cervical, breast, or prostate cancer. Patients with symptomatic central nervous system (CNS) metastases or asymptomatic CNS metastases requiring concurrent corticosteroid therapy were excluded from phase 1. For phase 2, patients with CNS metastases were excluded unless previously treated with surgery or radiotherapy and receiving therapy with stable, decreasing, or no steroids. All patients provided written informed consent in accordance with federal, local, and/or institutional guidelines.

Study Design

This open-label multicenter phase 1/2 study was conducted in 45 centers in the United States, Spain, Canada, and the United Kingdom. The study was conducted in accordance with the US Food and Drug Administration regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study was compliant with institutional review board and independent ethics committee requirements. The trial was registered at ClinicalTrials.gov (NCT01237678).

The phase 1 portion followed a traditional 3 + 3 dose escalation design exploring escalating doses of LM in combination with carboplatin/etoposide to determine the maximum tolerated dose (MTD). LM was administered as an intravenous (I.V.) infusion on days 1 and 8 of a 21-day cycle in combination with carboplatin/etoposide. This schedule was identical to that evaluated in a prior phase 1 monotherapy study in patients with CD56-positive myeloma (NCT00346255) and shown to have favorable tolerability. The starting dose of LM was 60 mg/m^2, which was 3 dose levels below the established MTD (112 mg/m^2) on this regimen; dose escalation proceeded, as tolerated, through 75 mg/m^2, 90 mg/m^2, and 112 mg/m^2. The starting dose of carboplatin was at an AUC (area under the plasma concentration vs. time curve) of 6; however, because of poor tolerability, this was reduced to an AUC of 5. Treatment continued for 4 cycles, with up to 6 cycles allowed. Patients

whose disease responded to treatment or patients with stable disease (SD) were eligible to receive single-agent LM treatment until disease progression or unacceptable toxicity. The MTD was determined on the basis of dose-limiting toxicities (DLTs) that occurred during cycle 1. A total of 12 patients were treated at the MTD to determine the recommended phase 2 dose (RP2D); after these patients had completed cycle 1, the phase 2 portion of the study commenced.

ED-SCLC patients participating in the phase 2 study were randomly assigned at a 2:1 ratio to arm 1 (LM + carboplatin + etoposide) or arm 2 (carboplatin + etoposide alone). Treatment in arm 1 proceeded as follows: intravenous LM on days 1 and 8 at the RP2D (initially 112 mg/m^2, reduced by protocol amendment to 90 mg/m^2), plus carboplatin I.V. at an AUC of 5 on day 1 and etoposide 100 mg/m^2 I.V. on days 1, 2, and 3 in each 21-day treatment cycle. In arm 2, carboplatin was administered at an AUC of 5 on day 1 and etoposide at a dose of 100 mg/m^2 on days 1, 2, and 3 of each 21-day treatment cycle. Carboplatin and etoposide were administered for up to 6 cycles as tolerated.

Assessments

Baseline assessments included medical history, vital signs, physical and neurologic examination, ECOG performance status, blood chemistry and hematology, serum pregnancy test, and electrocardiogram. During screening, radiologic imaging of the chest, abdomen, and pelvis (if applicable) was performed. In addition, baseline brain imaging (magnetic resonance imaging or computed tomography) and bone scans were required for all SCLC patients in order to determine the presence of brain metastases and bone involvement, respectively. Target and nontarget lesions were identified and recorded per RECIST version 1.1.[23]

All patients who received at least one dose of study drug and had at least one postbaseline safety assessment were included in the Safety Population analyses. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and monitored continuously throughout the study from the time of the first study dose until 28 days after treatment cessation.

Efficacy parameters included objective response rate (ORR), progression-free survival (PFS), and OS up to 12 months. Efficacy analyses were conducted on the intent-to-treat population (all patients who signed the informed consent and had at least one postbaseline efficacy evaluation). PFS was defined as the time from enrollment to disease progression via RECIST 1.1 or death for any cause. OS was defined as the time from enrollment to death or censored at the date last known to be alive.

Blood samples for pharmacokinetic characterization of LM, carboplatin, and etoposide were collected from all patients at prespecified time points during the first and fourth treatment cycles in phase 1. Plasma concentrations of LM (as well as total huN901 antibody) were assayed by enzyme-linked immunosorbent assay. Carboplatin and etoposide levels in plasma were measured by validated liquid chromatography–tandem mass spectrometry methods. Standard noncompartmental pharmacokinetic evaluation was performed by WinNonlin Professional 6.1.0.173 software (Pharsight, Mountain View, CA).

Statistical Analysis

The primary end point of phase 1 of the study was occurrence of DLTs as a function of the dose of LM when administered in combination with carboplatin + etoposide. No formal sample size calculation was performed for phase 1. The primary end point in phase 2 was PFS. For design purposes, the number of patients who were free of progression at 6 months was used to test hypotheses against historical 6-month PFS rates typically seen in patients treated with carboplatin + etoposide. Thus, the study was not powered to permit a statistically informative comparison of the randomized treatment groups with respect to PFS or OS. In phase 2, a 2-stage design was used, with 39 and 41 patients planned for treatment in the experimental arm in stages 1 and 2, respectively. For stage 1, if fewer than 18 patients were free of progression at 6 months, the trial was to be stopped and IMGN901 declared insufficiently active. On the basis of the estimated sample size (80 patients), the lower limit of the 1-sided 95% confidence interval (CI) for a 6-month PFS rate was equal to at least 40%.

Descriptive statistics for continuous variables were summarized using sample size, mean, median, standard deviation, minimum, and/or maximum. All descriptive analyses were performed by SAS statistical software version 9.2 or later (SAS Institute, Cary, NC). For the safety population evaluations, any event with the same onset date as start of study treatment or later was reported as treatment emergent. Baseline was defined as the last available assessment before day 1, cycle 1.

Time-to-event variables (PFS and OS) were analyzed by Kaplan-Meier estimates, including calculation of median and 95% CIs; the OS rate at 12 months and PFS rate at 6 months were also determined. All response-evaluable patients who had a postbaseline assessment were included in the ORR (confirmed and unconfirmed) and disease control rate (complete response [CR], partial response [PR], or SD) analyses, along with the corresponding exact 95% CIs based on the Clopper-Pearson method. Best overall responses (CR, unconfirmed CR, PR, unconfirmed PR, SD, or progressive disease) were tabulated.

Results

Patient Characteristics

Between November 2010 and May 2015, a total of 33 and 148 patients were enrolled onto the phase 1 and 2 portions of the study, respectively. For phase 2, a total of 98 patients were randomly assigned to arm 1 (LM + carboplatin + etoposide) and 50 to arm 2 (carboplatin + etoposide alone). Fifty-two patients enrolled onto arm 1 received LM at the RP2D of 112 mg/m^2; the remaining 46 were enrolled after a protocol amendment and received LM at 90 mg/m^2. Overall, 141 patients in phase 2 received at least one dose of study drug and had at least one postbaseline safety assessment and were included in the safety population (ie, n = 94 in arm 1 and n = 47 in arm 2). Patient baseline characteristics are summarized in Table 1. Extended details for the phase 1 population are presented in Supplemental Table 1 (in the online version).

The majority of patients enrolled onto the phase 1 portion of the study were women (61%), white (91%), and had a diagnosis of lung cancer (52%). The median age of this cohort was 59 years (range, 25-81 years). Most individuals had received prior systemic (82%) and/or radiotherapy (55%), and 42% had undergone surgery. For phase 2,

Table 1 Patient Demographic and Baseline Characteristics

Characteristic	Phase 1 (Carboplatin/ Etoposide + LM), Total	Phase 2			
		Arm 1			Arm 2
		Carboplatin/Etoposide + LM (112 mg/m^2)	Carboplatin/Etoposide + LM (90 mg/m^2)	Total	Carboplatin/ Etoposide
Number	33	50	44	94	47
Age, Years					
Median (range)	59 (25-81)	65.0 (43-80)	63.0 (43-90)	63.5 (43-90)	64.0 (40-82)
Gender					
Male	13 (39.4)	31 (62.0)	23 (52.3)	54 (57.4)	25 (53.2)
Female	20 (60.6)	19 (38.0)	21 (47.7)	40 (42.6)	22 (46.8)
Race[a]					
White	30 (90.9)	47 (98.0)	43 (97.7)	90 (95.7)	44 (93.6)
Black or African American	2 (6.1)	3 (6.0)	0	3 (3.2)	2 (4.3)
Asian	0	0	1 (2.3)	1 (1.1)	0
American Indian/Alaska Native	1 (3.0)	0	0	0	0
Unknown	0	0	0	0	1 (2.1)
ECOG PS					
0	14 (42.4)	13 (26.0)	9 (20.5)	22 (23.4)	12 (25.5)
1	19 (57.6)	32 (64.0)	30 (68.2)	62 (66.0)	32 (68.1)
2	-	5 (10.0)	5 (11.4)	10 (10.6)	3 (6.4)
Tobacco Smoking					
History of smoking	21 (63.6)	50 (100.0)	43 (97.7)	93 (98.9)	46 (97.9)
Currently smoking	6 (18.2)	19 (38.0)	16 (36.4)	35 (37.2)	13 (27.7)
Prior Therapy					
Surgery	14 (42.4)	0	2 (4.5)	2 (2.1)	2 (4.3)
Radiotherapy	18 (54.5)	1 (2.0)	9 (20.5)	10 (10.6)	3 (6.4)
Systemic therapy	27 (81.8)	0	0	0	1 (2.1)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: C/E = carboplatin/etoposide; LM = lorvotuzumab mertansine.
[a]Includes individuals of Hispanic or Latino origin.

demographic and baseline characteristics for the ED-SCLC patients were similar between arms. One patient in arm 2 had received one prior systemic therapy (5-fluorouracil plus leucovorin) for the treatment of colon cancer more than 3 years before study enrollment; the remaining 140 patients had received no prior systemic therapy.

Phase 1 Study: Exposure, Safety, and Efficacy

All 33 patients enrolled onto the phase 1 cohort were included in the analyses. Seven patients (21%) experienced a DLT in cycle 1, consisting primarily of hematologic toxicities. All 3 patients treated with 75 mg/m^2 LM and carboplatin at an AUC of 6 reported DLTs related to myelosuppression, including febrile neutropenia, thrombocytopenia, and granulocytopenia (grades 3 and 4). Therefore, the carboplatin dose was reduced to an AUC of 5, and escalation continued to the maximum planned LM dose of 112 mg/m^2. Only 2 of 12 patients reported a DLT at the 112 mg/m^2 dose level, and this dose was declared the RP2D.

The mean number of cycles that patients received during phase 1 was 4.3 (range, 1-10 cycles), with 55% receiving at least 4 cycles of therapy. Reduction of the carboplatin dose from an AUC of 6 to an AUC of 5 improved the overall tolerability of the combination regimen and resulted in a longer mean duration of dosing, greater number of cycles administered, and higher mean cumulative doses for patients receiving comparable LM doses.

All phase 1 patients experienced at least one treatment-emergent adverse event (TEAE), with gastrointestinal disorders and hematologic events being the most commonly reported. In addition, 58% of patients experienced at least one peripheral neuropathy event, including paresthesia, peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, neurotoxicity, and neuralgia, the majority of which were grade 1 or 2 in severity. The most commonly reported treatment-related TEAEs were anemia (55% of patients), peripheral sensory neuropathy (52%), thrombocytopenia (48%), fatigue (45%), and nausea (33%). Table 2 summarizes grade 3 and 4 treatment-related TEAEs reported for > 10% of patients. Thirty-three percent of the patients experienced at least one grade 4 TEAE; the most common were hematologic abnormalities, including thrombocytopenia (21%) and neutropenia (12%). In addition, grade 4 febrile neutropenia and leukopenia were observed in 3 patients each (9%).

Table 2 Incidence of Grade 3 and 4 Treatment-Related, Treatment-Emergent Adverse Events Reported in > 10% of Phase 1 Patients

Characteristic	Carboplatin (AUC 6) + Etoposide		Carboplatin (AUC 5) + Etoposide			Total
	+ LM 60 mg/m^2	+ LM 75 mg/m^2	+ LM 75 mg/m^2	+ LM 90 mg/m^2	+ LM 112 mg/m^2	
No. of TEAEs	6	6	3	6	12	33
No. of Patients With Any Treatment-Related TEAEs						
Grade 3	3 (50.0)	3 (50.0)	1 (33.3)	4 (66.7)	8 (66.7)	19 (57.6)
Grade 4	3 (50.0)	3 (50.0)	0	2 (33.3)	3 (25.0)	11 (33.3)
Thrombocytopenia						
Grade 4	2 (33.3)	2 (33.3)	0	2 (33.3)	1 (8.3)	7 (21.2)
Anemia						
Grade 3	1 (16.7)	2 (33.3)	0	2 (33.3)	2 (16.7)	7 (21.2)
Neutropenia						
Grade 3	2 (33.3)	0	0	1 (16.7)	2 (16.7)	5 (15.2)
Grade 4	0	1 (16.7)	0	1 (16.7)	2 (16.7)	4 (12.1)
Lymphocyte Count Decreased						
Grade 3	0	1 (16.7)	1 (33.3)	0	3 (25.0)	5 (15.2)
White Blood Cell Count Decreased						
Grade 3	0	1 (16.7)	0	0	4 (33.3)	5 (15.2)
Lymphopenia						
Grade 3	2 (33.3)	0	0	2 (33.3)	0	4 (12.1)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: AUC = area under the curve; LM = lorvotuzumab mertansine; TEAE = treatment-emergent adverse event.

During phase 1, TEAEs led to study treatment discontinuation in 24% of the patients, although no clear relationship with the study drug dose was seen. A low incidence (6%) of serious infections (sepsis) was observed in 2 patients enrolled onto phase 1; one case (grade 4) was considered possibly related to study drug, and the other was fatal but deemed unrelated to the study drug.

The confirmed ORR in the phase 1 population was 18%. All patients contributing to the ORR (4 cases of lung, 1 colon, and 1 ovarian cancer) had a confirmed PR, with no CRs observed. Thirty-six percent of the patients had SD; thus, the overall disease control rate was 64%.

Pharmacokinetics

A secondary objective of the phase 1 component was to determine LM pharmacokinetics when the triplet combination was provided to patients with solid tumors. Data for cycle 1 are presented that show that C_{max} and AUC values all increased in relative proportion to dose (Table 3), and an analogous profile was seen for total huN901 antibody measurements (data not shown). Day 1 and 8 concentration profiles were similar, and there was no apparent drug accumulation for these once-weekly doses. The mean apparent elimination half-life ($t_{1/2}$) of LM following the first drug

Table 3 Summary of Plasma Pharmacokinetic Parameters for Lorvotuzumab Mertansine After Infusion in Combination With Carboplatin and Etoposide (Cycle 1)

Dose Group (mg/m^2)	C_{max}, μg/mL	$t_{1/2}$, Hours	AUC_{0-t}, h*μg/mL	$AUC_{0-\infty}$, h*μg/mL
Cycle 1, Day 1				
60 (n = 6)	32.6 (4.4)	16.0 (1.0)	606 (106)	674 (97)
75 (n = 9)	39.7 (9.1)	17.5 (4.9)	752 (245)	947 (329)
90 (n = 6)	50.7 (5.0)	15.8 (2.1)	885 (192)	1033 (178)
112 (n = 12)	54.0 (14.5)	16.3 (2.2)	917 (202)	1090 (246)
Cycle 1, Day 8				
60 (n = 6)	31.9 (9.8)	15.9 (3.2)	444 (128)	728 (289)
75 (n = 9)	37.0 (5.9)	17.7 (3.8)	518 (108)	941 (162)
90 (n = 6)	47.5 (5.8)	15.0 (2.3)	657 (63)	1022 (120)
112 (n = 12)	46.8 (13.4)	15.0 (2.0)	627 (225)	1033 (227)

Data are presented as means (standard deviation).
Abbreviation: AUC = area under the curve.

Table 4 Summary of Treatment-Related Adverse Events (All Grades) in Phase 2 Safety Population (n = 141)

Characteristic	Arm 1, N (%)			Arm 2, N (%)
	C/E + LM (112 mg/m^2)	C/E + LM (90 mg/m^2)	Total[a]	C/E
Number	50	44	94	47
Any TEAE	50 (100.0)	44 (100.0)	94 (100.0)	46 (97.9)
Related TEAE	49 (98.0)	41 (93.2)	90 (95.7)	39 (83.0)
Any SAE	30 (60.0)	24 (54.5)	54 (57.4)	23 (48.9)
Related SAE	21 (42.0)	9 (20.5)	30 (31.9)	9 (19.1)
TEAEs leading to treatment discontinuation[b]	34 (68.0)	16 (36.4)	50 (53.2)	6 (12.8)
Any grade 3 or higher TEAE	48 (96.0)	44 (100)	92 (97.9)	42 (89.4)
Related grade 3 or higher TEAE	46 (92.0)	37 (84.1)	83 (88.3)	33 (70.2)
TEAE with outcome of death	7 (14.0)	11 (25.0)	18 (19.1)	3 (6.4)

Abbreviations: C/E = carboplatin/etoposide; LM = lorvotuzumab mertansine; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a]Includes patients treated at starting doses of LM of 112 and 90 mg/m^2.
[b]AEs are summarized only for subjects with primary reason for treatment discontinuation of adverse event.

administration was between 15.8 and 17.5 hours, and these values remained consistent across both dose level and intracycle dosing.

Phase 2 Study: Safety and Tolerability

The SCLC patients enrolled onto arm 1 received a mean of 5 cycles of study drug (range, 1-20 cycles). Sixty-six percent of the patients in arm 1 and 60% in arm 2 received at least 4 cycles of the study drug. As per protocol, no patient in arm 2 received more than 6 cycles. The initial 52 patients enrolled onto arm 1 received LM at the RP2D determined in phase 1 (112 mg/m^2); however, as a result of an increased frequency of peripheral neuropathy events in this population, the protocol was amended to increase the sample size, and 46 additional patients who were subsequently enrolled received LM at a reduced dose of 90 mg/m^2.

Serious adverse events (SAEs) were reported for 57% of patients in arm 1 and 49% in arm 2; of these, 32% and 19% were assessed as treatment related, respectively (Table 4). The most common SAEs observed among LM-treated patients were febrile neutropenia (6%), pneumonia (5%), neutropenia (3%), neutropenic sepsis (3%), peripheral sensory neuropathy (3%), and septic shock (3%). The prevalence of these SAEs was lower among patients treated with carboplatin/etoposide alone, with the exception of febrile neutropenia (11%) and diarrhea (4%). A total of 21 patients (18 enrolled onto arm 1 and 3 in arm 2) had a TEAE with an outcome of death. For 10 patients (9 in arm 1 and 1 in arm 2), the TEAE was an infection (either pneumonia or a septic event) deemed to be related to study drug (Supplemental Table 2 in the online version).

As shown in Table 4, almost all patients in the phase 2 study population (n = 141) experienced at least one TEAE. The most commonly observed TEAEs were gastrointestinal disorders and hematologic events, as well as general disorders and administration-site conditions. Treatment discontinuations due to TEAEs were higher among patients enrolled onto arm 1 (53%) compared to those reported among patients enrolled onto arm 2 (13%). The most common type of TEAEs leading to discontinuation were peripheral neuropathy events (29%). Of note, patients receiving LM at 90 mg/m^2 showed both a slightly lower overall incidence of peripheral neuropathy compared to those receiving LM at 112 mg/m^2 (73% vs. 86%) as well as fewer grade 3 events (11% vs. 36%).

The incidence of study treatment-related TEAEs was 96% in arm 1 and 83% in arm 2. Table 5 summarizes those reported for > 10% of the phase 2 SCLC population. Nervous system disorders were more frequently reported in patients who received LM (arm 1), including peripheral sensory neuropathy (61%) and paraesthesia (21%); patients enrolled onto arm 2 experienced a lower incidence of these events. Other treatment-related TEAEs occurring at a substantially higher incidence in arm 1 compared to arm 2 included fatigue, diarrhea, arthralgia, and increased alanine aminotransferase levels (Table 5). In total, 88% of arm 1 and 70% of arm 2 patients experienced a grade 3 or 4 TEAE that was deemed to be treatment related. The majority of grade 3 events were clinical laboratory abnormalities and included anemia (19%), peripheral sensory neuropathy (18%), neutropenia (17%), and thrombocytopenia (11%) (Supplemental Table 3 in the online version). Their incidence was similar in each arm, with the exception of peripheral sensory neuropathy, which occurred at a higher frequency in arm 1 compared to arm 2. Further, apart from neutropenia (32%), the occurrence of specific grade 4 TEAEs was low (< 6.5%).

Efficacy

For phase 2, efficacy analyses were performed on a total of 121 patients (82 in arm 1 and 39 in arm 2) as a result of a lack of postbaseline evaluations for 20 patients from the safety population. Median PFS was similar in both study arms: 6.2 months (95% CI, 5.4-7.2) for the combination regimen compared to 6.7 months (95% CI, 5.3-7.5) for carboplatin + etoposide alone (Figure 1A) with a hazard ratio of 0.93 (95% CI, 0.58-1.51). On the basis of Kaplan-Meier estimates, the median OS for arms 1 and 2 were 10.1 months (95% CI, 8.7-18.1) and 11.0 months (95% CI, 7.5-11.4), respectively (Figure 1B).

The ORR (confirmed and unconfirmed) for the 82 patients in arm 1 was 67% (95% CI, 55.8-77.1, with confirmed CR and PR rates of 4% and 61%, respectively) compared to 59% (95% CI, 42.1-74.4) for the 39 patients in arm 2 (Figure 2). The median time to confirmed responses in arm 1 was short (1.4 months), and the median duration of response was 6.1 months (95% CI, 4.9-7.1). Eleven patients (13%) had SD as best response; therefore the disease control rate, based on confirmed and unconfirmed best overall

Table 5 Common Treatment-Related, Treatment-Emergent Adverse Events (All Grades) Reported in > 10% of Phase 2 SCLC Patients

Characteristic	Arm 1, N (%)			Arm 2, N (%)
	C/E + LM (112 mg/m^2)	C/E + LM (90 mg/m^2)	Total	C/E
Number	50	44	94	47
Blood and Lymphatic System	41 (82.0)	33 (75.0)	74 (78.7)	31 (66.0)
Anemia	20 (40.0)	24 (54.5)	44 (46.8)	21 (44.7)
Febrile neutropenia	4 (8.0)	5 (11.4)	9 (9.6)	7 (14.9)
Leukopenia	5 (10.0)	3 (6.8)	8 (8.5)	6 (12.8)
Neutropenia	30 (60.0)	18 (40.9)	48 (51.1)	22 (46.8)
Thrombocytopenia	15 (30.0)	14 (31.8)	29 (30.9)	19 (40.4)
Gastrointestinal	38 (76.0)	28 (63.6)	66 (70.2)	23 (48.9)
Constipation	6 (12.0)	4 (9.1)	10 (10.6)	3 (6.4)
Diarrhea	14 (28.0)	11 (25.0)	25 (26.6)	6 (12.8)
Nausea	21 (42.0)	12 (27.3)	33 (35.1)	14 (29.8)
Vomiting	7 (14.0)	5 (11.4)	12 (12.8)	8 (17.0)
General Disorders and Administration Site	37 (74.0)	25 (56.8)	62 (66.0)	25 (53.2)
Asthenia	13 (26.0)	9 (20.5)	22 (23.4)	10 (21.3)
Fatigue	22 (44.0)	17 (38.6)	39 (41.5)	11 (23.4)
Mucosal inflammation	7 (14.0)	2 (4.5)	9 (9.6)	6 (12.8)
Infections and infestations	10 (20.0)	8 (18.2)	18 (19.1)	9 (19.1)
Investigations	24 (48.0)	18 (40.9)	42 (44.7)	15 (31.9)
Alanine aminotransferase increased	4 (8.0)	6 (13.6)	10 (10.6)	0
Neutrophil count decreased	5 (10.0)	6 (13.6)	11 (11.7)	7 (14.9)
Platelet count decreased	7 (14.0)	8 (18.2)	15 (16.0)	6 (12.8)
Metabolism and Nutrition System	19 (38.0)	19 (43.2)	38 (40.4)	18 (38.3)
Decreased appetite	15 (30.0)	9 (20.5)	24 (25.5)	15 (31.9)
Hypomagnesemia	3 (6.0)	8 (18.2)	11 (11.7)	1 (2.1)
Musculoskeletal and Connective Tissue	23 (46.0)	9 (20.5)	32 (34.0)	3 (6.4)
Arthralgia	9 (18.0)	2 (4.5)	11 (11.7)	0
Nervous System	45 (90.0)	31 (70.5)	76 (80.9)	11 (23.4)
Paraesthesia	14 (28.0)	6 (13.6)	20 (21.3)	2 (4.3)
Peripheral sensory neuropathy	32 (64.0)	25 (56.8)	57 (60.6)	2 (4.3)
Skin and Subcutaneous Tissue	18 (36.0)	8 (18.2)	26 (27.7)	16 (34.0)
Alopecia	13 (26.0)	6 (13.6)	19 (20.2)	16 (34.0)
Vascular disorders	7 (14.0)	5 (11.4)	12 (12.8)	3 (6.4)

Abbreviations: C/E = carboplatin/etoposide; LM = lorvotuzumab mertansine; SCLC = small-cell lung cancer.

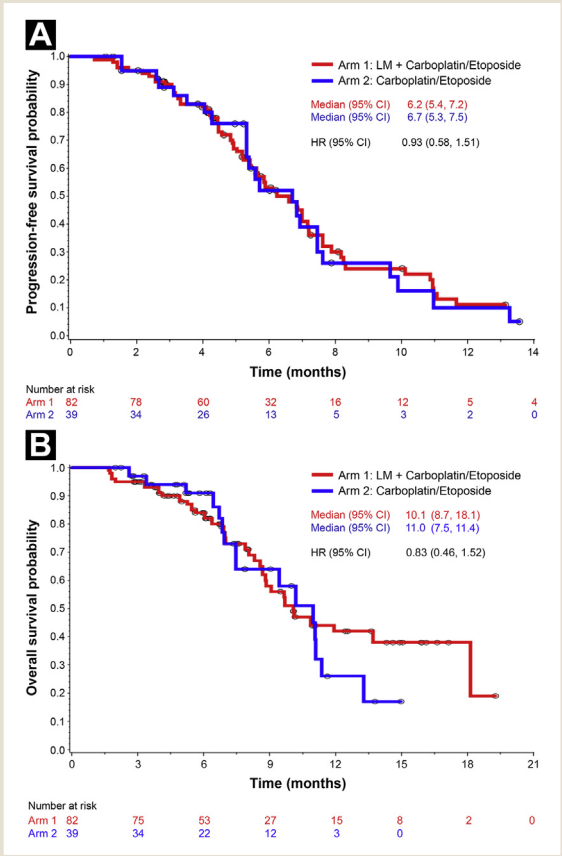
responses, was 92% in arm 1, which was comparable to the 95% observed for arm 2.

Discussion

Conventional chemotherapeutic approaches for the treatment of SCLC have largely reached a plateau of effectiveness, and the prognosis for individuals with metastatic disease remains dismal, with 2-year survival rates of less than 5%.[24] One strategy for improving patient outcomes is through the use of new drugs with novel mechanisms of action in combination with established first-line chemotherapy. In preclinical models, LM was shown to potentiate the antitumor activity of standard-of-care platinum/etoposide doublets in SCLC xenografts.[21] In addition, preliminary signs of efficacy were observed in SCLC patients who underwent LM monotherapy.[22] In light of these considerations, this multicenter phase 1/2 study was undertaken in order to evaluate the clinical activity and toxicity of LM in combination with carboplatin/etoposide chemotherapy in patients with ED-SCLC.

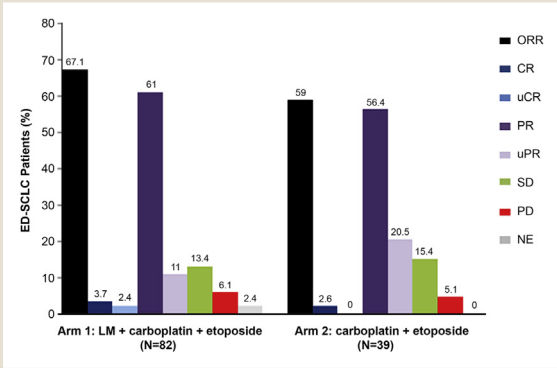
The phase 1 portion of the study accrued 33 patients with advanced solid tumors who had experienced disease progression despite prior therapy, the majority of which were lung cancers. The DLTs to emerge during the dose-finding stage consisted primarily of hematologic toxicities, including febrile neutropenia, thrombocytopenia, and granulocytopenia. Because myelosuppression is an established toxicity of carboplatin exposure in SCLC patients,[25] the carboplatin dose was reduced from an AUC of 6 to an AUC of 5. LM dose escalation then continued to the maximum planned dose of 112 mg/m^2, which was initially declared the RP2D; this was

Figure 1 Kaplan-Meier Curves for (A) Progression-Free and (B) Overall Survival



Abbreviations: CI = confidence interval; HR = hazard ratio.

Figure 2 Best Overall Response



Abbreviation: NE = not evaluable.

subsequently lowered to 90 mg/m^2 during phase 2 as a result of a higher incidence of peripheral neuropathy-associated AEs.

The TEAEs observed in both phases of the study were consistent with the previously reported profiles for single-agent LM as well as carboplatin/etoposide. In this regard, peripheral neuropathy was an expected AE, and the incidence seen in this study was comparable to that observed in a separate trial of multiple myeloma patients treated with LM in combination with lenalidomide and dexamethasone.[26] However, for phase 2, peripheral neuropathies were both the most commonly reported and the most common drug-related TEAEs leading to study discontinuation. Moreover, the frequency of events was notably higher in arm 1 compared to arm 2. These results suggest that combinations of LM with carboplatin, a drug itself known to cause peripheral neuropathy,[27] augment both the degree and severity of such symptoms in patients undergoing therapy.

On the basis of the safety results from earlier clinical trials evaluating LM, as either monotherapy or as part of combination regimens,[22,26] the high incidence and fatal outcomes of serious infection events in patients receiving the triple combination was unexpected. Myelosuppression is a known side effect of carboplatin, and it has been shown to increase susceptibility to infection.[25,28] However, serious infections and associated deaths were rare in the carboplatin/etoposide arm. The increase in fatal outcomes of serious infection events by the triplet combination underscored the challenges of combining agents with known hematologic toxicities. However, it is important to note that no relationship between LM dose and the infection rate was seen. However, it is clear that the triplet regimen is a risk factor because no serious infections were reported in patients receiving LM as single agent during the course of this trial.

The primary objective of the phase 2 portion of the study was to determine the efficacy of LM plus carboplatin/etoposide combination treatment in chemotherapy-naive patients with ED-SCLC. A minor improvement in response rate was seen in the combination arm (67%) relative to carboplatin/etoposide doublet therapy (59%), including more confirmed CRs and PRs. However, the median PFS for patients treated with the triplet combination was not significantly different from that seen for those in the carboplatin/etoposide-treated arm (6.2 vs. 6.7 months, respectively), and a projected improvement of 2.5 months from historical controls was not achieved. In terms of OS, median OS for combination-treated patients was 10.1 months, which falls in between the OS rates of 9.8 and 11 months reported for similar ED-SCLC patient populations.[29,30]

Conclusion

The addition of LM to carboplatin/etoposide doublet therapy failed to confer a significant PFS or OS advantage in previously untreated ED-SCLC patients. While the toxicities seen with combination treatment reflected those previously reported for LM and carboplatin, a higher incidence of serious infections with fatal outcomes was observed in patients receiving the triplet regimen. Thus, the addition of LM to a carboplatin/etoposide regimen administered on the schedule and doses evaluated here was associated with increased safety risks without a clear signal of benefit. This combination should not be considered for further development in ED-SCLC.

Clinical Practice Points

- The smoking-related malignancy SCLC remains a clinical challenge for the practicing oncologist, with the typical patient diagnosed being elderly and with many other comorbid illnesses.

- The standard of care remains platinum plus etoposide chemotherapy for 4 to 6 cycles, a modality that not changed the survival outlook for ED-SCLC patients in more than 2 decades. A number of strategies designed to improve survival outcomes have been explored, including the addition of a third drug to the platinum/etoposide combination; however, to date, none has provided meaningful clinical benefit with an acceptable rate of toxicity.
- LM is a CD56-targeting antibody-drug conjugate developed for tumor-selective delivery of the cytotoxic maytansinoid DM1. This phase 1/2 trial sought to integrate this novel agent into the carboplatin plus etoposide regimen in ED-SCLC. Unfortunately, no significant improvements in efficacy measures were observed, and SAEs leading to death were seen with the triplet combination.
- Improving outcomes in ED-SCLC will require new therapeutic strategies, beginning with a better understanding of the basic biologic pathways operative in this disease, which remain among the most recalcitrant malignancies seen in clinical practice.

Acknowledgments

The authors thank all the patients, their families, and investigators who participated in the trial. ImmunoGen Inc provided financial support for the conduct of the research and was involved in study design and the collection, analysis, and interpretation of data. We also thank Richard Bates for editorial assistance during the article's preparation.

Disclosure

D.N. is an employee of ImmunoGen Inc. The other authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.cllc.2016.09.002.

References

1. Semenova EA, Nagel R, Berns A. Origins, genetic landscape, and emerging therapies of small cell lung cancer. *Genes Dev* 2015; 29:447-62.
2. Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. *J Natl Compr Canc Netw* 2013; 11:8-98.
3. Hann CL, Rudin CM. Management of small-cell lung cancer: incremental changes but hope for the future. *Oncology (Williston Park)* 2008; 22:486-92.
4. Mamdani H, Induru R, Jalal SI. Novel therapies in small cell lung cancer. *Transl Lung Cancer Res* 2015; 4:533-44.
5. Singer L, Yom SS. Consolidative radiation therapy for extensive-stage small cell lung cancer. *Transl Lung Cancer Res* 2015; 4:211-4.
6. Cho SH, Kim HK, Jang HJ, et al. Modified one-day etoposide and cisplatin combination for previously untreated extensive-disease small-cell lung cancer: a retrospective evaluation of 36 cases. *Mol Clin Oncol* 2015; 3:914-8.
7. Foster NR, Qi Y, Shi Q, et al. Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage small-cell lung cancer: findings on the basis of North Central Cancer Treatment Group trials. *Cancer* 2011; 117:1262-71.
8. Niell HB, Herndon JE 2nd, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol* 2005; 23:3752-9.
9. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992; 10:282-91.
10. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994; 12:2022-34.
11. Lambert JM, O'Leary J, Whiteman KR, et al. Targeting CD56 (NCAM)-expressing neoplasms with lorvotuzumab mertansine. In: Phillips GL, ed. *Antibody–Drug Conjugates and Immunoglobulins: From Pre-clinical Development to Therapeutic Applications*. New York, NY: Springer; 2012:273-96.
12. Zeromski J, Nyczak E, Dyszkiewicz W. Significance of cell adhesion molecules, CD56/NCAM in particular, in human tumor growth and spreading. *Folia Histochem Cytobiol* 2001; 39(suppl 2):36-7.
13. Cunningham BA, Hemperly JJ, Murray BA, et al. Neural cell adhesion molecule: structure, immunoglobulin-like domains, cell surface modulation, and alternative RNA splicing. *Science* 1987; 236:799-806.
14. Kibbelaar RE, Moolenaar CE, Michalides RJ, et al. Expression of the embryonal neural cell adhesion molecule N-CAM in lung carcinoma. Diagnostic usefulness of monoclonal antibody 735 for the distinction between small cell lung cancer and non–small cell lung cancer. *J Pathol* 1989; 159:23-8.
15. Aletsee-Ufrecht MC, Langley K, Rotsch M, et al. NCAM: a surface marker for human small cell lung cancer cells. *FEBS Lett* 1990; 267:295-300.
16. Lantuejoul S, Moro D, Michalides RJ, et al. Neural cell adhesion molecules (NCAM) and NCAM-PSA expression in neuroendocrine lung tumors. *Am J Surg Pathol* 1998; 22:1267-76.
17. Tijink BM, Buter J, de Bree R, et al. A phase I dose escalation study with anti-CD44v6 bivatuzumab mertansine in patients with incurable squamous cell carcinoma of the head and neck or esophagus. *Clin Cancer Res* 2006; 12(20 pt 1):6064-72.
18. Chari RV, Martell BA, Gross JL, et al. Immunoconjugates containing novel maytansinoids: promising anticancer drugs. *Cancer Res* 1992; 52:127-31.
19. Erickson HK, Lambert JM. ADME of antibody–maytansinoid conjugates. *AAPS J* 2012; 14:799-805.
20. Ballantyne A, Dhillon S. Trastuzumab emtansine: first global approval. *Drugs* 2013; 73:755-65.
21. 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.
22. Shah MH, Lorigan P, O'Brien MER, 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.
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228-47.
24. Van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet* 2011; 378:1741-55.
25. Brahmer JR, Ettinger DS. Carboplatin in the treatment of small cell lung cancer. *Oncologist* 1998; 3:143-54.
26. Berdeja JG. Lorvotuzumab mertansine: antibody–drug-conjugate for $CD56^{+}$ multiple myeloma. *Front Biosci (Landmark Ed)* 2014; 19:163-70.
27. Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro Oncol* 2012; 14(suppl 4):iv45-54.
28. Ettinger DS. The role of carboplatin in the treatment of small-cell lung cancer. *Oncology (Williston Park)* 1998; 12(1 suppl 2):36-43.
29. Langer CJ, Albert I, Ross HJ, et al. Randomized phase II study of carboplatin and etoposide with or without obatoclax mesylate in extensive-stage small cell lung cancer. *Lung Cancer* 2014; 85:420-8.
30. Karam I, Jiang SY, Khaira M, et al. Outcomes of small cell lung cancer patients treated with cisplatin–etoposide versus carboplatin–etoposide. *Am J Clin Oncol* 2015; 38:51-4.

Supplemental Table 1 Patient Demographic and Baseline Characteristics for Phase 1 Study (Safety Population)

Characteristic	Carboplatin (AUC 6) + Etoposide		Carboplatin (AUC 5) + Etoposide			Total
	+ LM 60 mg/m^2	+ LM 75 mg/m^2	+ LM 75 mg/m^2	+ LM 90 mg/m^2	+ LM 112 mg/m^2	
Number	6	6	3	6	12	33
Age, Years						
Median (range)	55.0 (25-70)	70.0 (34-81)	63.0 (47-66)	59.0 (47-68)	54.5 (33-72)	59.0 (25-81)
Gender						
Male	4 (66.7)	2 (33.3)	2 (66.7)	1 (16.7)	4 (33.3)	13 (39.4)
Female	2 (33.3)	4 (66.7)	1 (33.3)	5 (83.3)	8 (66.7)	20 (60.6)
Race[a]						
White	6 (100)	4 (66.7)	3 (100.0)	5 (83.3)	12 (100.0)	30 (90.9)
Black or African American	0	1 (16.7)	0	1 (16.7)	0	2 (6.1)
American Indian/Alaska Native	0	1 (16.7)	0	0	0	1 (3.0)
Primary Tumor Site						
Lung	2 (33.3)	3 (50.0)	2 (66.7)	4 (66.7)	6 (50.0)	17 (51.5)
Colon	0	0	0	1 (16.7)	1 (8.3)	2 (6.1)
Ovary	0	1 (16.7)	1 (33.3)	0	0	2 (6.1)
Vulva	0	1 (16.7)	0	0	1 (8.3)	2 (6.1)
Kidney	1 (16.7)	0	0	0	0	1 (3.0)
Uterus	0	0	0	1 (16.7)	0	1 (3.0)
Cervix	0	0	0	0	1 (8.3)	1 (3.0)
Merkel-cell carcinoma	0	1 (16.7)	0	0	0	1 (3.0)
Scalp and neck	1 (16.7)	0	0	0	0	1 (3.0)
HNSCC	0	0	0	0	1 (8.3)	1 (3.0)
Thymus	0	0	0	0	1 (8.3)	1 (3.0)
Unknown	2 (33.3)	0	0	0	1 (8.3)	3 (9.1)
ECOG PS						
0	4 (66.7)	2 (33.3)	0	3 (50.0)	5 (41.7)	14 (42.4)
1	2 (33.3)	4 (66.7)	3 (100.0)	3 (50.0)	7 (58.3)	19 (57.6)
Tobacco Smoking						
No. with history of smoking	4	3	1	4	9	21
Currently smoking	1 (16.7)	1 (16.7)	0	2 (33.3)	2 (16.7)	6 (18.2)
Prior Therapy						
Surgery	1 (16.7)	3 (50.0)	2 (66.7)	2 (33.3)	6 (50.0)	14 (42.4)
Radiotherapy	3 (50.0)	4 (66.7)	0	4 (66.7)	7 (58.3)	18 (54.5)
Systemic therapy	5 (83.3)	6 (100.0)	2 (66.7)	5 (83.3)	9 (75.0)	27 (81.8)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: AUC = area under the curve; ECOG PS = Eastern Cooperative Oncology Group performance status; HNSCC = head and neck squamous-cell carcinoma; LM = lorvotuzumab mertansine.
[a]Includes individuals of Hispanic or Latino origin.

Supplemental Table 2 Treatment-Related Adverse Events in Phase 2 Study With Outcome of Death

Adverse Event	Arm 1 (N = 9)	Arm 2 (N = 1)
Neutropenic sepsis	1	0
Pneumonia	3	0
Sepsis	2	1
Septic shock	3	0

Supplemental Table 3 Common Grade 3 and 4 Treatment-Related, Treatment-Emergent Adverse Events Reported in > 10% of Phase 2 SCLC Patients

Characteristic	Arm 1, N (%)			Arm 2, N (%)
	C/E + LM (112 mg/m^2)	C/E + LM (90 mg/m^2)	Total	C/E
No. of TEAEs	50	44	94	47
Patients With Any Treatment-Related TEAEs				
Grade 3	37 (74.0)	33 (75.0)	70 (74.5)	30 (63.8)
Grade 4	24 (48.0)	21 (47.7)	45 (47.9)	21 (44.7)
Neutropenia				
Grade 3	12 (24.0)	4 (9.1)	16 (17.0)	8 (17.0)
Grade 4	17 (34.0)	13 (29.5)	30 (31.9)	13 (27.7)
Anemia				
Grade 3	8 (16.0)	10 (22.7)	18 (19.1)	10 (21.3)
Peripheral Sensory Neuropathy				
Grade 3	12 (24.0)	5 (11.4)	17 (18.1)	0
Thrombocytopenia				
Grade 3	4 (8.0)	6 (13.6)	10 (10.6)	5 (10.6)
Grade 4	4 (8.0)	2 (4.5)	6 (6.4)	5 (10.6)
Neutrophil Count Decreased				
Grade 4	2 (4.0)	4 (9.1)	6 (6.4)	6 (12.8)
Febrile Neutropenia				
Grade 3	1 (2.0)	2 (4.5)	3 (3.2)	6 (12.8)

Abbreviations: C/E = carboplatin/etoposide; LM = lorvotuzumab mertansine; SCLC = small-cell lung cancer; TEAE = treatment-emergent adverse event.