Phase I/II Trial of Custirsen (OGX-011), an Inhibitor of Clusterin, in Combination with a Gemcitabine and Platinum Regimen in Patients with Previously Untreated Advanced Non-small Cell Lung Cancer

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Purpose: Clusterin (CLU), an antiapoptotic, stress-associated protein, confers resistance to therapy when overexpressed. This trial tested custirsen (OGX-011), an inhibitor of CLU protein production, combined with gemcitabine/platinum in patients with advanced non-small cell lung cancer (NSCLC).

Patients and Methods: This was a single-arm, multicenter, phase I/II study in chemotherapy-naive stage IIIB/IV NSCLC. Custirsen was infused during a loading dose period and weekly in combination with gemcitabine (1250 mg/m^2) on days 1 and 8 and with cisplatin (75 mg/m^2) or carboplatin (area under the curve 5) on day 1 of each 21-day cycle. Ten patients were treated in a phase I lead-in and 71 in the phase II component. The primary efficacy endpoint was response rate, with exploratory analyses of other efficacy outcomes and biomarker relationships.

Results: Eighty-one patients received custirsen and were included in the primary analysis. The median age was 61 years; 82% had stage IV disease. Overall response was 25 of 81 (31%; 95% confidence interval 21–42). The 1- and 2-year survivals were 54 and 30%, respectively. Toxicity of the combination was not appreciably different from what is reported for gemcitabine/platinum combinations. Custirsen treatment decreased serum CLU levels in 95% of patients evaluated. Patients who achieved a minimum median CLU level for the population of ≤38 μg/ml during treatment had a median survival of 27.1 compared with 16.1 months for patients who did not ($p = 0.02$).

Conclusion: Based on the above results, a randomized phase 3 trial to evaluate the survival benefit of custirsen in patients with NSCLC is warranted.

Key Words: Advanced NSCLC, Antisense oligonucleotide, Novel therapeutics, Chemotherapy, Biomarker.

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Development of resistance to chemotherapy commonly occurs during treatment of cancers. One pathway to resistance is the up-regulation of pro-cell-survival proteins that seem to promote tumor progression and facilitate tumor resistance by inhibiting apoptosis.[1] One such protein is clusterin (CLU), an antiapoptotic, stress-associated protein that is cytoprotective and confers resistance to treatment when overexpressed.[2–6] More than 70% of human non-small cell lung cancers (NSCLCs) are positive for CLU by immunohistochemistry.[7,8]

In preclinical and prior clinical trials, custirsen sodium (OGX-011; OncoGenex Technologies Inc., Vancouver, BC, Canada), a second generation antisense oligonucleotide (ASO), has been shown to decrease the expression of CLU in cancer cells by hybridizing CLU mRNA and inhibiting production of CLU protein.[9,10] Custirsen has a 21-mer phosphorothioate backbone similar to first-generation ASOs.[11] However, the addition of methoxyethyl groups affords increased affinity for the target mRNA, increased potency, and prolonged tissue half-life, allowing for weekly dosing.[9,10] Custirsen has been shown to decrease CLU expression in A549 cells by greater than 75% in a dose-dependent, sequence-specific manner.[7] Custirsen suppression of CLU also enhanced sensitivity to chemotherapies such as paclitaxel and gemcitabine both in vitro and in vivo in several lung cancer models.[7,12] In vivo studies demonstrated significant delay in

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tumor growth in A549 xenografts when custirsen plus chemotherapy was compared with chemotherapy alone.[9]

Prior studies have looked at the prognostic role of CLU in NSCLC. In one, the expression of CLU was significantly related to pathologic differentiation, clinical stage, and lymph node metastasis but not to sex or histologic type.[8]

Supported by preclinical data that custirsen significantly decreases CLU production, increases sensitivity of lung cancer cells to chemotherapies, and delays growth of cancers in lung cancer models, this phase I/II study was designed to assess safety and response rate, as the primary objectives, when custirsen was combined with gemcitabine/platinum as first-line therapy in patients with chemotherapy-naive, IIIB/IV NSCLC. Secondary objectives included progression-free survival (PFS), overall survival (OS), and the effect of custirsen on serum CLU levels. Exploratory analyses evaluated the association of serum CLU changes with survival outcome.

PATIENTS AND METHODS

Patient Eligibility

Patients with NSCLC were eligible if they had histologically/cytologically confirmed IIIB (N3 and/or pleural or pericardial effusion) or IV disease not amenable to treatment with curative intent. No prior chemotherapy or biological therapy was allowed, but patients could have received prior radiation therapy providing that: the lesion used for response determination had not been previously irradiated or had increased in size since radiotherapy; radiotherapy had been completed at least 2 weeks before treatment (6 weeks for lesions used to determine response); and the patient had recovered from all toxicities. Additional eligibility requirements included: age $\geq$18 years; at least one unidimensionally measurable lesion meeting RECIST criteria[13]; an Eastern Cooperative Oncology Group performance status (PS) of $\leq$1; and adequate hematologic, hepatic, and renal function. Patients were excluded if they were pregnant, had leptomeningeal disease or untreated central nervous system metastases, active infection, serious systemic disorder, or second malignancy. Written informed consent was required. The study was approved by ethical committees at all participating institutions and filed with the U.S. Food and Drug Administration as an Investigational New Drug Application and with Health Canada as a Clinical Trial Application.

Study Design and Treatment

Prior phase I studies showed that 640 mg of custirsen was the biologically effective dose, that is, the dose at which tumors demonstrated a 92% reduction of CLU mRNA,[10] and that custirsen was well tolerated in conjunction with docetaxel chemotherapy.[14] Thus, the current trial was initiated with a 10-patient safety phase I lead-in to assess pharmacokinetics (PK) and tolerability of custirsen with cisplatin/gemcitabine. Three patients were treated at the 480-mg and seven patients at the 640-mg target dose. The starting dose of custirsen was 640 mg for patients in the phase II part of the study.

Patients could receive up to six cycles of therapy. Custirsen was infused intravenously (IV) over 2 hours during a loading dose period (three doses on days -7, -5, and -3) and then weekly on days 1, 8, and 15 of each 21-day cycle. Gemcitabine (1250 mg/m^2) was infused IV over 30 minutes on days 1 and 8 and cisplatin (75 mg/m^2) over 1 hour on day 1. Carboplatin (area under the curve of 5) was allowed as an alternative to cisplatin in the phase II portion. Doses were to be held or reduced for both chemotherapy and custirsen for the following: febrile neutropenia, grade 4 neutropenia lasting $\geq$7 days, grade 4 thrombocytopenia, bleeding with $\geq$grade 2 thrombocytopenia, grade 4 nausea and vomiting, grade 3 partial thrombin time/international normalized ratio, $\geq$grade 3 aspartate amino-transferase or alanine amino-transferase, $\geq$grade 2 bilirubin, serum sodium $<$125 mmol/liter, creatinine clearance $<$35 ml/min, or any other grade 3/4 toxicity other than alopecia. There were separate dose modifications for gemcitabine for stomatitis and diarrhea. Therapy was discontinued if more than two dose reductions were required or if there was more than a 2-week delay in therapy because of toxicity. All patients received standard supportive care and blood product support. Hematologic growth factors were permitted.

Study Assessments

Baseline evaluations included a history and physical examination, PS, routine biochemical, hematologic and coagulation analyses, and a pregnancy test, if applicable. Baseline tumor assessments included computer tomography scans of the chest, abdomen, and pelvis, plus bone scans when clinically indicated. Tumor assessments were performed following cycles 2, 4, and 6 and subsequently every 2 months until disease progression, initiation of new anticancer therapy or death.

Safety evaluations included monitoring of vital signs during custirsen infusions, and repeat baseline evaluations were performed during the first loading dose visit, on day 1 only or days 1 and 8 of each cycle of therapy, and at an "End of Treatment" visit. Adverse events (AEs) and concomitant medications were recorded at each weekly visit and 30 days after the last dose of study treatment. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for AEs V3.0. Once treatment was discontinued, safety assessments were obtained at each disease evaluation visit until disease progression. An independent medical oncologist reviewed all available information for safety after the first 43 patients were enrolled in phase II.

In both the phase I and II parts of the study, serum CLU samples were collected at baseline and on day 1 of cycles 2 and 3 before any treatment. Samples were analyzed at Mayo Clinical Trial Services (Rochester, MN) using a solid-phase, enzyme-linked immunosorbent assay (ELISA) in microplate format designed for the quantitative measurement of human CLU in serum and plasma (BioVendor Clusterin ELISA, Ann Arbor, MI).

Blood samples for custirsen, gemcitabine, and cisplatin PK studies were collected from all phase I patients at fixed times with a total of eight samples starting at 0.5 hours and ending at 24 hours. Quantitation of custirsen was analyzed by

a hybridization-dependent nuclease ELISA at Charles River Laboratories. Quantitation of gemcitabine and cisplatin in plasma was analyzed by high-performance liquid chromatography mass spectrometry at the Prostate Center at Vancouver General Hospital Investigational Drug Program.

Statistical Considerations

The primary objective of the study was to estimate the proportion of patients responding (complete response [CR] and partial response [PR] to custirsen in combination with gemcitabine/platinum. It was assumed that the combination being evaluated would be of further interest if the data supported a true response probability of >20%.[15] The accrual target was 70 evaluable patients (phase I and II). The phase II portion of the study included a futility test when 43 eligible and evaluable patients had been accrued. Rejection of the futility null hypothesis corresponded to 5 or fewer responses (11.6% or less responding). The primary analysis population was defined as all patients treated with study drug. The worst degree of toxicity experienced by a patient during the study was computed. Tumor response and disease progression were based on RECIST.[16] PFS was defined as the time from the date of first study treatment to the date of documented disease progression or death. For patients without disease progression who initiated subsequent anticancer therapy, the date of progression was defined as the date of new cancer treatment. PFS was censored at the date of the first study treatment for patients who failed to return for disease assessments and at the last disease assessment for patients who were still alive without disease progression at the end of the study. OS was defined as the time from the date of first study treatment to the date of death from any cause; OS time was censored at the date of last contact for patients who were still alive.

Proportional hazard regression analyses were performed to assess the relationship between survival and serum CLU levels. Only patients with a baseline and at least one CLU level during treatment were included in the analyses (i.e., the CLU analysis population). During treatment, a CLU response was defined as having a minimum CLU level less than or equal to the median minimum CLU level for the population (≤38 μg/ml). The starting survival model included the following terms: baseline CLU (categorized as below and above the median baseline CLU for the population), CLU response, and any interaction. The model reported is the result of a step-down procedure using a 0.1 criteria for exclusion of terms.

To evaluate the robustness of the conclusion, a 30-day (approximately cycle 2, day 1) landmark analysis was also performed where only patients with CLU data available at the day-30 landmark were included in the analysis to reduce the bias related to censoring because of early withdrawal. Ideally, these analyses should be performed using proportional hazard modeling with a time-dependent covariate, as was done in a previous phase II study in patients with prostate cancer that evaluated serial CLU[17]; however, the data collected after cycle 2 in this study were too sparse to allow this type of analysis. To assess the consistency of the results between this study and the previous prostate cancer study, analyses were performed on the CLU analysis population for a CLU response defined as achieving a "threshold" minimum CLU level ≤45 μg/ml during treatment (a threshold target defined from the previous prostate cancer study).

Finally, Kaplan-Meier (KM) estimates for all patients evaluable in the CLU analysis population ($n = 55$) and for the 30-day landmark subpopulation ($n = 49$) were plotted for CLU responders versus nonresponders. Survival by the above-described classification was compared using a median estimate and the log-rank test.

RESULTS

Patient Demographics and Disease Characteristics

Eighty-five patients were enrolled between November 2004 and November 2006 at 15 sites in the United States and Canada. All patients have been followed for a minimum of 3 years. In the phase I safety component of the study, three patients were treated with custirsen at a dose of 480 mg and seven patients at 640 mg. Higher doses were not tested. Three of 10 achieved a PR. As there was no dose-limiting toxicity, the dose for the phase II portion was set at 640 mg. On the basis of evaluation performed after the first 43 patients were enrolled and the observation that 13 of the 43 patients (30%) had an objective response, the study was continued as planned. Subsequently, 32 more patients were enrolled.

Table 1 shows the baseline characteristics. The median age was 61 years and 51% were male. The majority of patients had stage IV disease (81%) and an Eastern Cooperative Oncology Group PS of 1 (68%).

Treatment

Of the 85 patients entered on trial, 81 received at least one dose of study drug and were included in the primary analysis. Four patients never received study drug because of decreased PS (2), positive pregnancy test (1), and cerebro-

TABLE 1. Patient Demographics and Disease Characteristics at Baseline

Characteristic	$n = 81$
Age (yr), median (range)	61 (43–79)
Gender (%)	
Male	51
Female	49
Stage (%)	
IIIB	19
IV	81
Visceral metastases (%)	23
Histology (%)	
Adenocarcinoma	51
Squamous cell	16
Undifferentiated/unspecified NSCLC	33
ECOG performance status (%)	
0	32
1	68
Prior radiation therapy (%)	31

NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

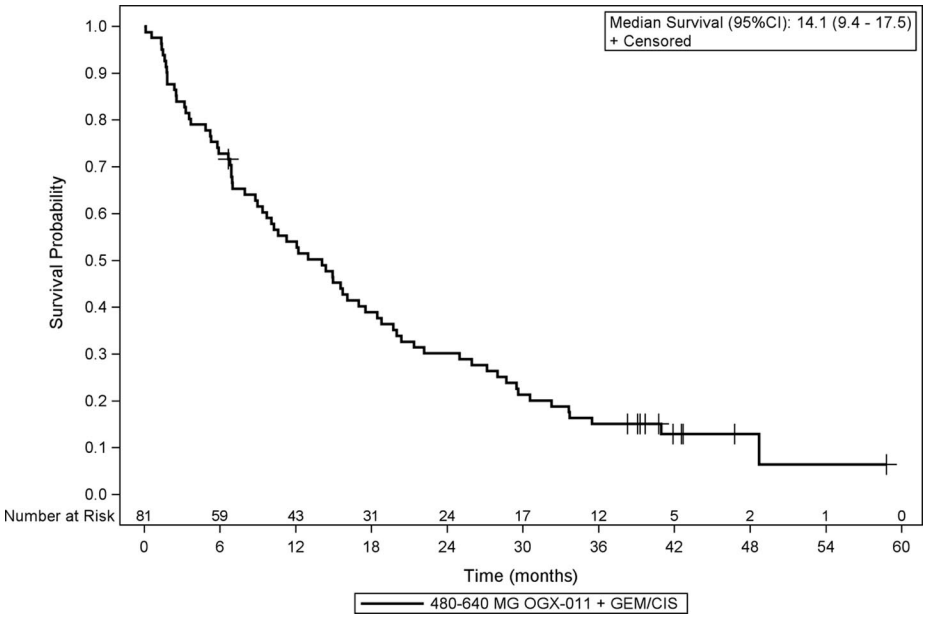

FIGURE 1. Kaplan-Meier survival curve for all patients ($n = 81$).

vascular accident (CVA) during screening (1). Seventy-five of 81 (93%) patients received custirsen and at least one dose of chemotherapy. Six were removed from study before the start of chemotherapy for disease progression (2), withdrawal of consent (1), and AEs (3) but were included in the primary analyses. Sixty of 75 (80%) patients who received chemotherapy initially received cisplatin and 15 (20%) received carboplatin. Nine of 60 (15%) on cisplatin were switched to carboplatin because of an AE. Sixty-one of 81 (75%) patients discontinued study drug before the end of cycle 6: 21 (26%) for disease progression, 11 (14%) at the discretion of the treating physician, 5 (6%) for withdrawal of consent, 23 (28%) as the result of an AE, and 1 (1%) died. The most common AEs causing discontinuation of study drug were hematologic toxicity and fatigue. The mean relative dose intensity was 92% for custirsen, 85% for gemcitabine, and 94% for the two platinum compounds.

Information on treatment after progression was prospectively collected and available for all patients. For the 46 (57%) who received second-line chemotherapy, the median time to treatment was 2.6 months from the last study drug administration. For these 46 patients, treatment included erlotinib (16 patients), docetaxel regimen (12 patients), and pemetrexed regimen, gemcitabine/platinum regimen, and "other" (6 each).

Efficacy

Tumor response to custirsen in combination with gemcitabine/platinum occurred in 25 of 81 (31%) patients (95% confidence interval [CI] 21–42), with 1 CR and 24 PRs. Fifty-six (69%; 95% CI 58–79) had a clinical response (objective response and stable disease). Thus, the estimate of the proportion of patients responding met the prespecified success criterion of being consistent with a greater than 20% probability of response. The median PFS was 4.3 months (95% CI 3.0–5.3) and OS was 14.1 months (95% CI 9.4–17.5; Figure 1). One- and 2-year KM survival rates were 54% (95% CI 43–64) and 30% (95% CI 21–40), respectively. There were no significant differences in the response rate or PFS when the three patients in the phase I portion of the trial who received a lower dose of custirsen (480 mg) were removed from the analysis. Because two of the three patients in the 480 mg group had very long survival times, the median survival did change from 14.1 ($n = 81$) to 13.0 months ($n = 78$), but the 1- and 2-year survival rates remained unchanged.

Toxicity

Fourteen (1%) custirsen infusions were interrupted or discontinued, and 1% were modified for toxicity. During the initial loading dose period, in which custirsen was administered without chemotherapy, symptoms of chills and pyrexia were seen in approximately half the patients; 96% were grade 1 or 2.

The three AEs during this loading dose period causing removal from study treatment were hypotension after infusion, increased liver enzymes, and myocardial infarction. Infusion reactions were not seen outside the initial loading dose period.

The most common treatment-related nonhematologic AEs, in decreasing order, included nausea, fatigue, chills, pyrexia, vomiting, decreased appetite, dysgeusia, alopecia, and constipation. Eighty-six percent were grade 1 or 2. There were two uncommon AEs: thrombotic thrombocytopenic purpura (reported to be associated with gemcitabine[18]) and acute cortical blindness (reported to be associated with cisplatin[19,20]). Table 2 lists all hematologic and nonhematologic ≥grade 3 AEs seen in ≥5% of patients. The most common serious AEs requiring hospitalization were pleural effusion, dyspnea, and CVA.

Hematologic toxicity was frequently observed. The degree of hematologic toxicity appeared to vary with the platinum agent administered, with more grade 4 neutropenia

TABLE 2. Grade 3 or Higher AEs Observed in ≥5% of Patients by Toxicity Grade ($n = 81$)

Toxicity[a]	Grade 3 (%)	Grade 4 (%)
Neutropenia[b]	30	21
Leukopenia[b]	40	6
Thrombocytopenia[b]	11	22
Lymphopenia[b]	32	1
Hyponatremia[b]	22	1
Dyspnea	20	
Fatigue	16	
Anemia[b]	14	
Vomiting	11	
Hypokalemia[b]	10	1
Nausea	10	
Pleural effusion	7	
Pulmonary embolism	2	5
Elevated ALT[b]	6	
Decreased appetite	6	
Arthralgia	5	
Chest pain	5	
Hypophosphatemia[b]	5	
Hypoxia	4	1

[a] Percent of patients experiencing an event.
[b] Laboratory events based on actual laboratory values recorded.
AE, adverse event.

and thrombocytopenia in patients treated with carboplatin. Febrile neutropenia was documented in three patients; serious infections (pneumonia, empyema, bacteremia, and septicemia) in four; and grade 3 hemorrhage (epistaxis and gastrointestinal bleed) in two. The incidence of treatment with hematopoietic growth factors was 15% and with platelet transfusions was 10%.

Four patients died within 90 days of study entry due to septicemia (1), myocardial infarction (1), cardiac-related event (1), and stroke (1). Only the septicemia was deemed to be possibly related to study therapy.

Serum Clusterin Correlations with Survival

Serum CLU samples were collected at baseline and before treatment on day 1 of cycles 2 and 3. Of the 81 patients, 69 had baseline CLU levels and 55 of 69 also had at least one CLU assessment during treatment and were included in the CLU analysis population.

Baseline CLU levels.

The baseline mean and standard error and the baseline median for CLU in the CLU analysis population were 65.2 ± 3.7 μg/ml and 54.0 μg/ml, respectively. For the 14 patients who only had CLU levels at baseline, the mean and standard error and the median for CLU were 62.7 ± 4.8 μg/ml and 57.5 μg/ml, respectively.

CLU levels during treatment.

Custirsen treatment significantly reduced serum CLU levels by day 1 of cycle 2 or 3, with 52 of the 55 patients (95%) having a reduction in CLU during treatment compared with their baseline level. The mean reduction from baseline was 25.1 μg/ml, $p < 0.0001$ (baseline versus minimum CLU during treatment, paired t test).

CLU levels and survival analyses.

For the 69 patients with baseline serum CLU levels, median survival was 14.9 months. Missing levels during treatment in the 14 patients who had only baseline CLU levels were primarily due to study discontinuation before cycle 2. As expected, these 14 patients had a worse survival, with a median survival time of 2.4 months, compared with 18.8 months for the 55 patients who reached at least day 1, cycle 2.

Baseline CLU was not found to be a prognostic variable, that is, it was not associated with survival when evaluated in all 69 patients with a baseline CLU level, in 55 patients who had both baseline and at least 1 CLU assessment during treatment (CLU analysis population), or in the 49 patients evaluable for the 30-day landmark analysis (30-day landmark subpopulation). The model resulting from the step-down selection for the analyses included only CLU response as an independent variable. Figure 2 shows the Kaplan-Meier estimates for both the CLU analysis population and the 30-day landmark subpopulation regarding CLU responders and nonresponders. For both analyses, the estimated ratio of death hazard rate for those classified as having a CLU response to the death hazard rate for those not having a response was 0.5, representing a 50% reduction in the hazard of death with a CLU response.

When the analysis was repeated for the CLU analysis population using another CLU response definition from a previous prostate cancer study (i.e., achieving a "threshold" minimum CLU level ≤45 μg/ml during treatment), the results remained the same (Table 3) and showed a consistently longer survival time for patients having a CLU response. Of the 55 patients in the CLU analysis population, 35 (64%) achieved a threshold minimum serum CLU level of ≤45 μg/ml during treatment and had a median survival of 27.1 months compared with the 20 (36%) who did not achieve a threshold minimum CLU level of ≤45 μg/ml and had a median survival of 15.6 months ($p = 0.02$).

Custirsen Pharmacokinetic Studies

The mean $AUC_{0\text{-inf}}$ was 149.4 μg·h/ml for the 480-mg dose and 260.7 μg·h/ml for the 640-mg dose. Clearance was 3.3 and 2.5 liter/h, respectively. The terminal half-life was 3.7 hours at the 640-mg dose. CLU was quantifiable in all postdose samples for up to 25.5 hours. Gemcitabine and cisplatin PK profiles seemed not to be affected by the addition of custirsen.

DISCUSSION

Lung cancer remains the leading cause of cancer death in North America.[21] We tested a strategy to target acquired chemotherapy resistance resulting from stress-induced up-regulation of cytoprotective molecular chaperones like CLU. CLU has multiple mechanisms of action that promote cell survival and confer broad-spectrum treatment resistance. As examples, CLU is involved in the inhibition of endoplasmic

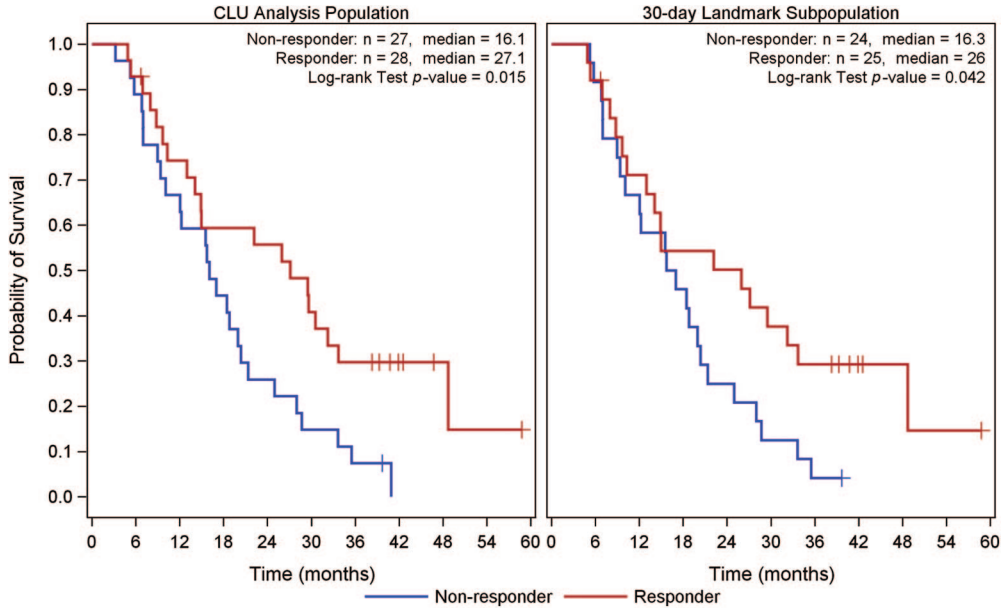

FIGURE 2. Survival analyses of patients with and without a clusterin (CLU) response during treatment Kaplan-Meier estimates for the CLU analysis population and the 30-day landmark subpopulation for CLU responders and nonresponders.

TABLE 3. Effect of Serum Clusterin Responses on Survival

CLU Response Definition	Population	CLU Response Outcome	Patients (*n*)	Median Survival (mo)	Hazard Ratio (95% CI)	Log-Rank test (*p* value)
Median minimal level ≤38 μg/ml	CLU analysis population	Responder	28	27.1	0.5 (0.3–0.9)	0.02
		Nonresponder	27	16.1		
	30-d landmark subpopulation	Responder	25	26.0	0.5 (0.3–1.0)	0.04
		Nonresponder	24	16.3		
Threshold level ≤ 45 μg/ml	CLU analysis population	Responder	35	27.1	0.5 (0.3–0.9)	0.02
		Nonresponder	20	15.6		

CLU, clusterin; CI, confidence interval.

reticulum vacuolization and protein aggregation under stress[22,23]; interaction with and inhibition of activated Bax[24]; and enhancement of COMMD1 and Ik-B degradation, thereby enhancing nuclear factor-kB transcriptional activity.[25,26]

Custirsen is a second-generation ASO to CLU mRNA. A major limitation of first-generation ASOs was the requirement for continuous IV infusion because of the short tissue half-life. The stability and efficacy of second-generation ASOs has been improved by modifications of the phosphodiester linkage.[27] The formation of duplexes with RNA with significantly higher affinity and with improved resistance against nuclease-mediated metabolism results in improved tissue half-life.[28]

In this study, custirsen was administered in combination with a gemcitabine/platinum doublet as first-line therapy for advanced NSCLC. Unlike many studies, survival data are mature with a minimum follow-up of 3 years. The median OS was 14.1 months, and the 1- and 2-year survivals were 54 and 30%, with 12% still alive for a median of 41 (range 38–59) months. The major limitation of this study is the lack of a comparator arm. However, the survival data in this multicenter trial compare quite favorably with published data of patients receiving a gemcitabine/platinum-based regimen in a similar dose and schedule, with median survivals of 7 to 11 months, 1-year survival rates of 37 to 43%, and 2-year survival rates of <20%.[29–37]

Exploratory analyses were performed on survival and changes in serum CLU levels from baseline during custirsen treatment. CLU levels decreased in 95% of patients after custirsen treatment, by an average of 25.1 μg/ml (35%; $p < 0.0001$). This is not an isolated finding as custirsen had a notable effect on lowering serum CLU in three prior studies in patients with prostate cancer.[10,14,17] Most importantly, achieving a serum CLU response even after only one cycle of therapy, defined as achieving levels ≤38 μg/ml (the median minimal level for the population) was shown to be associated with a reduced risk of death of 50% (hazard ratio of 0.5). In addition, using the serum threshold level of ≤45 μg/ml as identified in the phase 2 study in prostate cancer, was also associated with longer survival, suggesting that this effect is not isolated to one tumor type.[17] Larger randomized phase III

studies in NSCLC will be required to determine whether lowering serum CLU is correlated with improved survival and what, if any, minimal levels are required to observe a survival benefit.

As anticipated from a regimen containing gemcitabine and a platinum agent, hematologic toxicity was frequently observed, and grade 4 toxicity was more common in patients treated with carboplatin, but few patients required growth factor or platelet support. Other toxicities of the combined regimen were not felt to be appreciably different than those reported for previously published gemcitabine/platinum doublets.[29–37] Ninety-six percent of infusion reactions were grade 1 and 2, and reactions only occurred during the 9-day loading dose period when custirsen concentrations were highest. Vascular events (CVA, myocardial infarction, pulmonary embolus, and deep vein thrombosis), common findings in up to 18% of chemotherapy-treated patients with advanced NSCLC,[38] were seen in 15% of patients. Grade 3/4 lymphopenia, seen in 33% of patients, has been reported as a class effect of ASOs but with no reported clinical sequelae.

CONCLUSION

The effect of custirsen treatment on serum CLU levels validates the physiologic on-target activity of custirsen. Demonstrating the potential survival benefit of custirsen in patients with NSCLC will require results from a larger randomized phase 3 study, similar to the phase 3 studies currently evaluating custirsen in patients with metastatic, castrate-resistant prostate cancer.

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