Randomized, phase IIb study of low-dose cytarabine and lintuzumab *versus* low-dose cytarabine and placebo in older adults with untreated acute myeloid leukemia

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ABSTRACT

Improving outcomes in older adults with acute myeloid leukemia remains a formidable challenge. Lintuzumab (SGN-33; HuM195) is a humanized monoclonal antibody directed against CD33, which is expressed on the majority of myeloblasts in acute myeloid leukemia. The primary objective of this randomized, double-blinded, placebo-controlled trial was to determine whether addition of lintuzumab to low-dose cytarabine would increase overall survival in adults aged 60 years and over with untreated acute myeloid leukemia. Randomization was stratified by age, previous hematologic disorder, and performance status. All patients received cytarabine (20 mg subcutaneously twice daily) on Days 1-10 of each 28-day cycle. Patients received lintuzumab (600 mg) or placebo intravenously once weekly in Cycle 1 and once every other week in Cycles 2-12. A total of 211 patients (107 lintuzumab, 104 placebo) were randomized. Median age was 70 years (range 60-90). Survival was not significantly prolonged with lintuzumab treatment (hazard ratio 0.96; 95% confidence interval (CI) 0.72-1.28; P=0.7585). Median survival was similar between treatment arms (4.7 months lintuzumab *vs.* 5.1 months placebo) and in the subgroup of patients with high-risk cytogenetics (4.5 months). Infusion-related reactions, predominantly Grades 1-2, occurred more commonly in the lintuzumab arm (51% *vs.* 7% placebo); no other clinically significant difference in safety was noted. These results confirm that lintuzumab in combination with low-dose cytarabine did not prolong survival and that low-dose cytarabine remains a valid comparator for trials of non-intensive therapies in older patients with acute myeloid leukemia, regardless of cytogenetic profile.
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Introduction

Acute myeloid leukemia (AML) is a disease of older adults, with a median age at diagnosis of 66 years in the USA.[1] The median survival for treated and untreated AML patients from one Medicare study was two months,[2] and for older AML patients undergoing remission induction chemotherapy on cooperative group studies ranged from 3.5 to nine months, depending on prognostic factors such as age, cytogenetics, and performance status.[3-6]

The benefit of remission induction chemotherapy in older adults is not clear-cut. Inferior outcome is often attributed to distinct disease biology, including higher rates of adverse cytogenetic and molecular abnormalities, chemotherapy resistance, and chemotherapy intolerance, related either directly to drug toxicity, or indirectly through concomitant comorbidities, which are more prevalent in an older population.[7-10] While some prospective, retrospective, and population-based studies suggest a survival advantage with intensive chemotherapy compared to low-dose therapy or best supportive care,[11-13] others report no benefit or even a survival detriment.[14,15] Given the high cost of induction therapy for hospitalized patients, transfusion requirements, and the compromised Quality of Life, it is entirely reasonable for older adults to opt for less-intensive approaches.[16]

Common, low-dose chemotherapy options include hypomethylating agents such as azacitidine or decitabine, or low-dose (LD) cytarabine. Azacitidine has demonstrated a survival benefit compared to best supportive care or low- or high-dose chemotherapy in a subgroup analysis of patients with less than 30% blasts.[17] Encouraging phase II data support the use of decitabine in older AML patients,[18,19] though it did not demonstrate superior survival compared to best supportive care/LD cytarabine in a randomized phase III trial.[20] When compared to older AML patients receiving hydroxyurea, those treated with LD cytarabine had an improved rate of complete remissions (CR) (18% *vs.* 1% hydroxyurea; P=0.0006), which accounted for improved overall survival (12-month survival approx. 24% *vs.* approx. 6% hydroxyurea) among 217 patients randomized in the National Cancer Research Institute AML14 Trial.[21] LD cytarabine can, therefore, be considered an appropriate control for clinical studies of new investigational agents.

CD33 is an attractive therapeutic target for AML because it

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is expressed on the majority of myeloblasts, whereas expression on normal tissues appears to be limited to cells of the myeloid and monocytic lineages.[22-25] Antitumor activity has been previously demonstrated by gemtuzumab ozogamicin (GO), an immunoconjugate consisting of a recombinant humanized anti-CD33 antibody conjugated to the cytotoxic agent calicheamicin. In a study of nearly 500 patients recently presented in abstract form, addition of GO to LD cytarabine significantly improved the rate of CR (30% *vs*. 16% LD cytarabine alone; *P*=0.0005), though addition of GO did not improve 12-month survival (27% *vs.* 28% LD cytarabine alone).[26] However, the role of GO for upfront therapy of AML has not been established and it is not currently available in the USA, due to safety concerns raised in the pivotal Southwest Oncology Group (SWOG) study.[27]

Lintuzumab (SGN-33; HuM195) is a humanized monoclonal antibody directed against CD33. *In vitro*, lintuzumab binds CD33 and has multiple mechanisms of action, including the induction of effector function through complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cellular cytotoxicity mediated by natural killer cells.[28,29] Lintuzumab also inhibits inflammatory cytokine production via direct signaling.[29]

Lintuzumab monotherapy has previously been investigated in patients with AML, myelodysplastic syndromes (MDS), and other myeloid malignancies, revealing limited toxicity (primarily infusion-related reactions) and modest anti-leukemic activity when administered for four consecutive days, every two weeks.[30,31] A subsequent randomized, phase III trial to assess the benefit of adding lintuzumab to induction chemotherapy (mitoxantrone, etoposide, and cytarabine, MEC) in relapsed/refractory AML failed to demonstrate an improvement in CR rate with the addition of lintuzumab, although toxicity was not increased in the lintuzumab arm.[32] In a phase I dose-escalation trial to address whether significantly higher concentrations of lintuzumab (at doses of 1.5-8 mg/kg/week x 5 weeks, then every other week thereafter) would be tolerated over extended periods of time and would result in greater therapeutic activity, serum lintuzumab exposures were up to 20-fold higher than those obtained in the lower-dose trials, and responses were observed in 7 of 17 patients with AML (41%), including 4 CRs. Consistent with the lower-dose trials, mild infusion-related reactions were the most common adverse event (AE).[33]

The primary objective of this phase IIb, randomized, double-blinded, placebo-controlled trial was to determine whether addition of lintuzumab to LD cytarabine would provide a survival benefit in older adults with previously untreated AML. Secondary end points included platelet and RBC transfusion requirements, infections/fevers requiring hospitalization or intravenous (iv), antibiotics, serial peripheral blood counts, protocol-defined clinical benefit, and Quality of Life. As this represents the largest completed study of the experience of older AML patients prospectively treated with LD cytarabine, exploratory pooled and subgroup analyses are presented.

Design and Methods

Patients

Eligible patients were adults at least 60 years old with untreated AML (as defined by the World Health Organization, excluding patients with acute promyelocytic leukemia or chronic myeloid leukemia) that occurred *de novo* after exposure to chemotherapy for a separate malignancy, or evolved from a previous hematologic disorder. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or under, white blood cell count less than $30x10^9$/L, at least 20% blasts in either bone marrow or blood, and 50% or over of leukemic blasts expressing CD33. Hydroxyurea was permitted prior to treatment on study to control peripheral blast counts. No bone marrow biopsies or aspirates were required at study entry; AML diagnoses were confirmed centrally using slides from the initial diagnosis, either from a bone marrow biopsy or aspirate (if performed) or from peripheral blood (if circulating blasts were present). Risk groups were assigned according to Fröhling *et al.*[34] and Wheatley *et al.*[35] Immunophenotyping was performed centrally. Cytogenetic analyses were conducted at local laboratories and confirmed centrally. After being informed of the potential benefits and risks of available treatment options, all patients must have declined intensive chemotherapy.

The study was approved by the Institutional Review Board of each study center and written informed consent was obtained from all patients prior to any study-specific procedures, in accordance with the Declaration of Helsinki.

Study design and treatment

This was an international, phase IIb, parallel, randomized, double-blinded, placebo-controlled trial that evaluated survival in older patients with previously untreated AML. Patients were randomly assigned in a 1:1 ratio to receive either LD cytarabine in combination with lintuzumab or LD cytarabine in combination with placebo. Randomization was stratified by age (<70 years or ≥70 years), history of previous hematologic disorder (yes or no), and ECOG performance status (0-1 or 2). The stratified randomization (block size = 4) was performed by Datatrak.

The primary objective of the study was to determine whether combination treatment with LD cytarabine and lintuzumab conferred a survival benefit over treatment with LD cytarabine and placebo. The primary efficacy end point was overall survival (OS), as by consensus of the steering committee, OS was felt to be the most relevant end point. Secondary end points were platelet and RBC transfusion requirements, infections/fevers requiring hospitalization or iv antibiotics, and serial peripheral blood counts. Additionally, Quality of Life was assessed using the Functional Assessment of Cancer Therapy, Leukemia (FACT-Leu).[36] Bone marrow biopsies were not required in this trial, as they were felt to represent a substantial discomfort and inconvenience to older AML patients. Thus, in place of remission status as a marker of drug activity, protocol-defined clinical benefit (i.e. no peripheral blasts, ANC $>1.0x10^9$/L, platelets $>100x10^9$/L, and no transfusions for one week) was evaluated. Safety assessments included evaluation of adverse events and routine hematology and serum chemistry tests. An independent data monitoring committee, including oncologists and a statistician experienced in clinical trials, monitored patient safety on an ongoing basis according to a formal charter.

Patients could receive up to twelve 28-day cycles of therapy. During each treatment cycle, patients received cytarabine (20 mg subcutaneously twice daily, based on the AML14 trial)[21] on Days 1-10. For Cycle 1 only, patients received study drug (lintuzumab 600 mg or placebo) iv once weekly (on Days 1, 8, 15 and 22). For all subsequent cycles, patients received lintuzumab or placebo iv once every other week (on Days 1 and 15). Patients were pre-medicated with acetaminophen and diphenhydramine or equivalent prior to each infusion, and received additional pre-medication,

consisting of methylprednisolone or dexamethasone, prior to the first infusion. Routine pre-treatment with corticosteroids was discouraged for subsequent infusions unless a patient previously experienced a Grade 3 infusion reaction. After treatment was completed, patients remained on study and were followed until death or study closure.

Supportive care in accordance with the National Comprehensive Cancer Network (NCCN) guidelines for AML (e.g. prophylactic antimicrobial therapy, transfusions of red blood cells (RBC) and platelets, and hematopoietic growth factors) was recommended. The sponsor distributed the NCCN guidelines to clinical centers and provided broad-spectrum antibiotics, growth factors, and support for transfusions, to help minimize differences in standard of care in this international study.

Details of the statistical analysis are available in the *Online Supplementary Appendix*.

Results

Patients' characteristics

Data for this study were collected from November 2007 to August 2010. A total of 211 patients (107 lintuzumab, 104 placebo) were randomized at 72 international clinical centers: 103 patients (49%) at 36 centers in Europe (Austria, Bosnia and Herzegovina, Bulgaria, Hungary, Lithuania, Poland, Romania, Serbia, and Ukraine), 70 patients (33%) at 24 centers in Russia, and 38 patients (18%) at 12 centers in the USA.

Median age of patients in the ITT population was 70 years (range 60-90 years); 56% were at least 70 years of age, and 8% were at least 80 years of age (Table 1). Almost half (47%) were male and 98% were Caucasian, 45% had a baseline ECOG status of 2, and 23% had a history of previous hematologic disorder. The median percentage of CD33-positive blasts in bone marrow or blood was 95.1% (range 51-100%). Cytogenetic risk group assignment[34] included 42% standard risk and 41% high risk. Using the Wheatley prognostic score,[35] 68% of patients were categorized as poor risk, 24% as standard risk, and 9% as good risk.

The treatment arms were balanced in most characteristics. The proportion of patients with baseline blast percentage of 30% or over was higher in the lintuzumab arm (83% *vs.* 65% placebo; P=0.0039) and the mean baseline WBC count (x 10^9/L) was higher in the lintuzumab arm (10.9 *vs.* 7.2 placebo; P=0.0170). Minor differences were also observed between treatment arms in the cytogenetic risk group, with a higher proportion of patients in the lintuzumab arm categorized as high risk (48% *vs.* 35% placebo); however, the difference between treatment arms was not statistically significant.

Twenty-two patients (9 lintuzumab, 13 placebo) were randomized with incorrect stratification factors (i.e. age, previous hematologic disorder, or ECOG performance status). Stratified analyses using both the stratification factors entered at randomization and the actual stratification factors documented at baseline resulted in the same conclusions as in the primary unstratified analysis. The treatment arms appeared to be balanced across actual stratification factors.

Efficacy results from the randomized trial

At the time of study termination, 187 patients (89%) had died, including one patient who had not received treatment (Figure 1). Twenty-two patients (14 lintuzumab, 8 placebo) remained in follow up and one patient from each group withdrew consent; data for these 24 patients were censored for the primary efficacy analysis of OS. The estimated median survival for the lintuzumab arm was 4.7 months compared to 5.1 months for the placebo arm, and there appeared to be no difference in the survival rate at each pre-specified time point (1, 3, 6, 9, 12, 15 and 18 months) between the 2 treatment arms. Twelve-month OS was 28% for the lintuzumab arm and 26% for the placebo arm. Survival was not significantly prolonged with lintuzumab plus LD cytarabine compared to placebo plus LD cytarabine (Figure 2A): hazard ratio 0.96 (95% CI: 0.72-1.28; P=0.7585). This result, equivalent to a 4% decrease in the hazard of death for patients in the lintuzumab arm, was not statistically significant at the 0.31 (two-sided) level, indicating that lintuzumab was unlikely to be associated with a positive treatment effect.

Subgroup analyses of OS did not identify a subset of patients who benefited from lintuzumab: the hazard ratios for most subgroups were close to 1 (Figure 3). The 95% confidence intervals included 1, with the exception of the subgroup of patients with less than 75% CD33-positive blasts. In this subgroup, the estimated hazard ratio was 0.4; the disparity is most likely due to the small number of patients (n=29). The hazard ratio for patients with previous hematologic disorder was 0.58, suggesting a potential lintuzumab treatment effect in this small subgroup (n=49); however, the 95% confidence interval included the value 1.

No formal comparisons of secondary efficacy end points were performed, as the primary end point was not statistically significant at the pre-specified level. However, no clinically meaningful differences were observed in any of the secondary efficacy end points. The rates of platelet transfusions (28.4 per patient year lintuzumab *vs.* 28.3 placebo) and RBC transfusions (27.7 per patient year lintuzumab *vs.* 26.8 placebo) were similar. Sixty-eight percent of patients in each treatment arm had infections or fevers requiring hospitalization or iv antibiotics; the rate was 3.9 per patient year in the lintuzumab arm *vs.* 3.7 in the placebo arm. No consistent patterns of changes were observed for ANC, platelet count, hemoglobin, or percentage of blasts; the median change from baseline was similar for both treatment arms, and the range of values for the 2 treatment arms overlapped considerably at each time point.

No clinically meaningful differences were apparent for additional efficacy end points. No consistent pattern of change in FACT-Leu score was observed; the median change from baseline was similar for both treatment arms and the range of values for the 2 treatment arms overlapped considerably at each time point. Protocol-defined clinical benefit (i.e. no peripheral blasts, ANC >1.0x10^9/L, platelets >100x10^9/L, and no transfusions for one week) was experienced by 29 patients (27%) in the lintuzumab arm and 30 patients (29%) in the placebo arm.

Overall, 99% of patients in this international study were hospitalized at least once. Reasons for hospitalization varied according to regional standards. For example, administration of LD cytarabine required hospitalization at some study centers. Thus, common reasons for hospitalization included study-related procedures (67% of hospitalizations) and transfusions (20% of hospitalizations). The proportion of hospitalizations for adverse events was

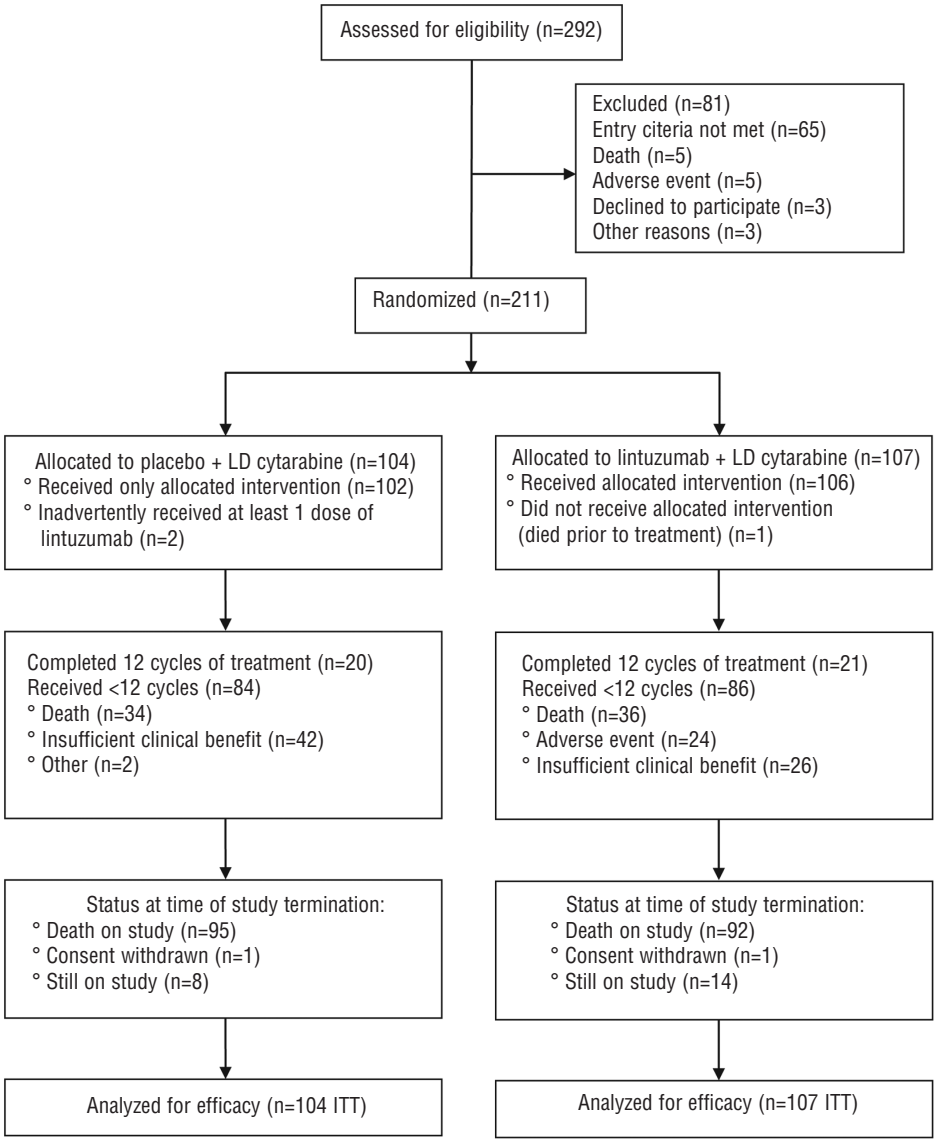

Figure 1. ITT population.

similar between treatment arms (17% lintuzumab *vs.* 15% placebo).

Safety results from the randomized trial

A total of 210 patients received at least one dose of study drug, and 41 patients completed 12 cycles of study treatment: 21 (20%) in the lintuzumab arm and 20 (19%) in the placebo arm (Figure 1). The median number of treatment cycles received was 4.0 (range 1-12). The median number of treatment cycles (4.0 lintuzumab, 3.0 placebo) and the total duration of exposure (46.7 patient years lintuzumab, 45.9 patient years placebo) were comparable between treatment arms. Compliance with cytarabine dosing was generally good: 195 patients (93%) received at least 75% of planned doses over all treatment cycles. The proportion of patients receiving at least 75% of planned cytarabine doses was typically over 95% for individual cycles.

Seventy patients (33%) discontinued study treatment due to death (34% lintuzumab, 33% placebo). In addition, 24 patients (22%) had an AE leading to discontinuation of treatment in the lintuzumab arm, compared to 6 patients (6%) in the placebo arm. Adverse events that led to treatment discontinuation for more than one patient were AML progression (7 patients, 3%), pneumonia (3 patients, 1%), cerebral hemorrhage (2 patients, 1%), and hypersensitivity (2 patients, 1%). With the exception of one patient in the placebo arm who discontinued treatment due to cerebral hemorrhage, all these events occurred in the lintuzumab arm.

In general, there appeared to be no difference in the incidence of AEs between the study arms. The most common AEs were thrombocytopenia (42%), AML progression (36%), pyrexia (32%), neutropenia (32%), anemia (31%), febrile neutropenia (28%), nausea (23%), and pneumonia (23%). Notable treatment-emergent AEs that were observed in a higher proportion of patients in the lintuzumab arm were cough (18% *vs.* 11% placebo), chills (21% *vs.* 4% placebo), peripheral edema (14% *vs.* 8% placebo), dyspnea (14% *vs.* 5% placebo), hypotension

Table 1. Patients' characteristics (ITT population).

Characteristics	Placebo + LD cytarabine (N = 104)	Lintuzumab + LD cytarabine (N=107)	*P* value* (N=211)	Total (N=211)
Age, y				
Median (range)	71.0 (60, 87)	70.0 (60, 90)	0.2240	70 (60, 90)
≥70 y, n. (%)	61 (59)	58 (54)	0.5791	119 (56)
≥80 y, n. (%)	11 (11)	6 (6)	0.2131	17 (8)
Sex, n. (%)			0.4920	
Male	52 (50)	48 (45)		100 (47)
Female	52 (50)	59 (55)		111 (53)
ECOG status, n. (%)			1.0000	
0	7 (7)	8 (7)		15 (7)
1	50 (48)	51 (48)		101 (48)
2	47 (45)	48 (45)		95 (45)
AML by WHO classification, n. (%)		0.7995		
AML with MDS-related changes†	31 (30)	29 (27)	60 (28)	
AML with recurrent genetic abnormalities	5 (5)	4 (4)	9 (4)	
AML, not otherwise categorized	68 (65)	74 (69)	142 (67)	
Antecedent hematologic disorder, n. (%)	28 (27)	21 (20)	0.2541	49 (23)
Baseline WBCx10^9/L				
Median (range)	4.6 (0, 32)	4.2 (1, 74)	0.0170	4.3 (0, 74)
Category, n. (%)			0.0540	
0 to 9.9	73 (70)	63 (59)		136 (64)
10 to 49.9	23 (22)	30 (28)		53 (25)
50 to 99.9	0	4 (4)		4 (2)
>100	0	0		0
Not available	8 (8)	10 (9)		18 (9)
Baseline percentage of blasts, n. (%)‡		0.0039		
<20%	3 (3)	0		3 (1)
20-<30%	33 (32)	18 (17)		51 (24)
≥30%	68 (65)	89 (83)		157 (74)
Percent CD33-positive blasts, median (range)	94.4 (55, 100)	95.4 (51, 100)	0.2761	95.1 (51, 100)
Cytogenetic risk group, n. (%)§		0.1311		
Low risk	1 (1)	0		1 (0)
Standard risk	46 (44)	42 (39)		88 (42)
High risk	36 (35)	51 (48)		87 (41)
Not available	21 (20)	14 (13)		35 (17)
Wheatley Prognostic Score, n. (%)¶		0.2590		
Good risk	12 (12)	6 (6)		18 (9)
Standard risk	22 (21)	28 (26)		50 (24)
Poor risk	70 (67)	73 (68)		143 (68)

**Fisher's exact test was used to evaluate categorical variables; the t-test was used to evaluate continuous variables. †2008 WHO classification.[37] Data were originally reported using the 2002 criteria,[38] as AML with multilineage dysplasia (n=56) and AML with myelodysplastic syndrome (n=4). ‡Entry criteria allowed baseline percentage of blasts to be determined from either bone marrow or blood. §Cytogenetic risk was determined at baseline according to Fröling 2006.[34] ¶Wheatley prognostic score[35] is a composite score comprising age, ECOG performance status, cytogenetic risk group, WBC count at diagnosis, and* de novo versus *secondary AML.*

(11% *vs.* 5% placebo), pain in extremity (10% *vs.* 3% placebo), hyperthermia (8% *vs.* 2% placebo), and hypersensitivity (8% *vs.* 0% placebo); these events were likely associated with infusion-related reactions to lintuzumab. Relative risk of the most common adverse events is shown in Figure 4.

Overall, 89% of patients had at least one Grade 3 or over AE (90% lintuzumab, 87% placebo). With the exception of AML disease progression, reported for 35% of patients overall, the most common adverse events Grade 3 or over were thrombocytopenia (36%), anemia (22%), neutropenia (22%), febrile neutropenia (20%), and pneumonia (12%) (Table 2). There seemed to be no clinical difference in incidence of Grade 3 or over treatment-emergent AEs between the study arms.

The proportion of patients with at least one dose interruption was higher in the lintuzumab arm (45% *vs.* 4% placebo). Infusion-related reactions, predominantly Grades 1-2, were reported for 55 patients (51%) in the lintuzumab arm and 7 patients (7%) in the placebo arm. The most common infusion-related AEs in the lintuzumab arm were chills (21 patients, 19%) and pyrexia (11 patients, 10%). Other infusion-related AEs reported for at least 5% of patients in the lintuzumab arm were dyspnea, hypersensitivity, hypertension, hyperthermia, and hypotension (6 patients, 6% each) and vomiting (5 patients, 5%).

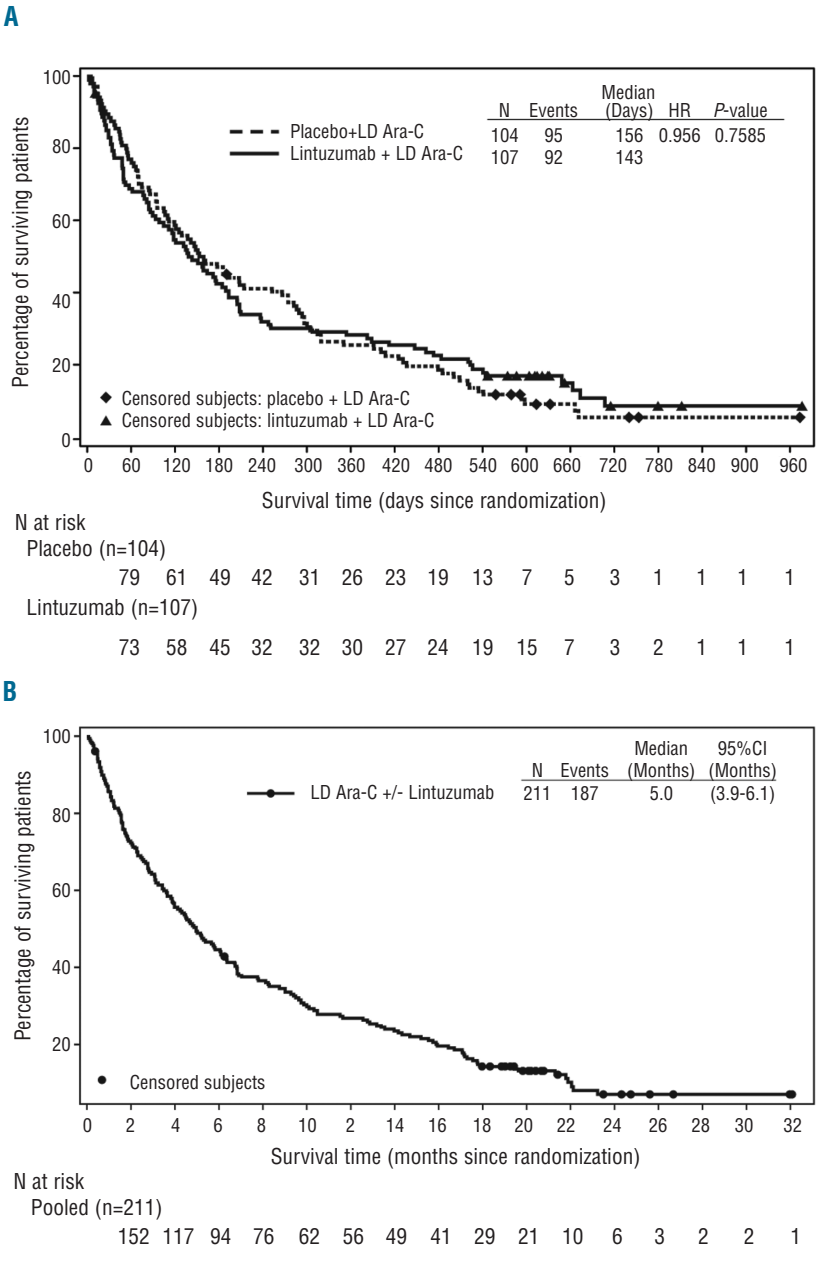

Figure 2. Overall survival. Overall survival (A) by treatment arm and (B) for the pooled population (n=211) over approx. 32 months.

Analysis of the pooled study population

Analyses conducted for the pooled study population (n=211) included OS and the effects of cytogenetic risk group, age, and pooled previous hematologic disorder on OS. Overall survival for the pooled study population (n=211) was 5.0 months (95% CI: 3.9-6.1) (Figure 2B).

Thirty-six patients were excluded from the analysis of pooled cytogenetic risk group: data for 35 patients were unavailable (33 due to poor or no growth) and there was a single patient in the low-risk group. The median OS in patients with standard risk cytogenetics was 8.7 months (95% CI: 4.3-10; n=88), compared with 4.5 months in patients with high-risk cytogenetics (95% CI: 2.8-5.7; n=87); hazard ratio 1.63 (95% CI: 1.19-2.25; *P*=0.0024). Evaluation of the effect of age under 70 years *versus* 70 years or over for the pooled study population yielded a median OS for patients under 70 years of age of 5.5 months (95% CI: 3.8-7.0; n=92), compared with 4.8 months for those 70 years or over (95% CI: 3.4-6.2; n=119); hazard ratio 1.15 (95% CI: 0.86-1.54; *P*=0.3524).

History of previous hematologic disorder did not affect survival in the pooled population. The median OS was 5.0 months (95% CI: 3.6-6.8; n=49) for patients with previous hematologic disorder and 5.0 months (95% CI: 3.6-6.3; n=162) for those without; hazard ratio 1.09 (95% CI: 0.78-1.52; *P*=0.6122).

Discussion

Improving outcomes amongst older adults with AML remains a formidable challenge, related to resistant disease biology and poor tolerance of therapy, highlighting the need for more novel and less toxic regimens. Monoclonal

Table 2. Adverse events ≥ Grade 3 occurring in at least 5% of patients overall (safety population).

Adverse event	Placebo + LD cytarabine (N=102)* n. (%)	Lintuzumab + LD cytarabine (N = 108)* n. (%)	Total (N=210)* n. (%)
Thrombocytopenia	36 (35)	39 (36)	75 (36)
AML progression	32 (31)	42 (39)	74 (35)
Anemia	25 (25)	22 (20)	47 (22)
Neutropenia	26 (25)	21 (19)	47 (22)
Febrile neutropenia	18 (18)	23 (21)	41 (20)
Pneumonia	10 (10)	16 (15)	26 (12)
Leukopenia	10 (10)	7 (6)	17 (8)
Sepsis	8 (8)	9 (8)	17 (8)
Asthenia	7 (7)	4 (4)	11 (5)
Pyrexia	6 (6)	5 (5)	11 (5)
Hypokalemia	4 (4)	6 (6)	10 (5)

**A total of 211 patients were randomized in the study (107 lintuzumab, 104 placebo). Of these, 210 patients received at least one dose of study drug; one patient randomized to lintuzumab died before receiving treatment. Two patients in the placebo arm inadvertently received at least one dose of lintuzumab. Thus 102 patients received placebo only and 108 patients received at least one dose of lintuzumab.*

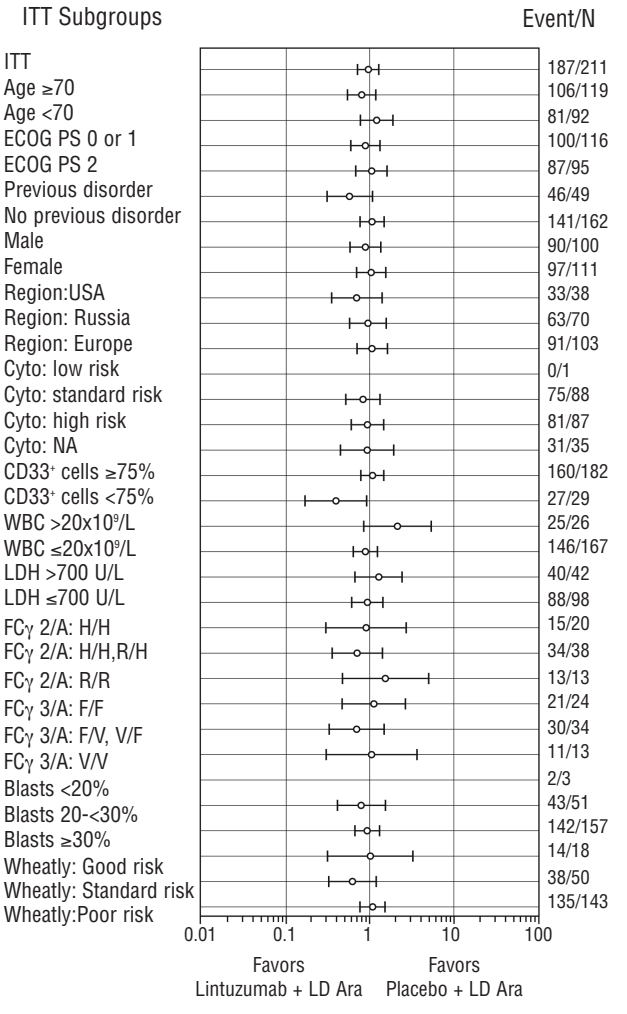

Figure 3. Subgroup analysis: hazard ratios for overall survival by treatment arm. Hazard ratio with 95% confidence interval is displayed for each prognostic factor.

antibody therapy directed against CD33 is an attractive strategy, given the frequency of CD33 expression in AML,[39,40] its presence upon leukemia-initiating cells,[41] and its potential importance as an inhibitory receptor in cellular activation processes.[42,43] Indeed, attempts to supersaturate CD33 with monoclonal antibodies have been undertaken in an attempt to induce leukemic cell death independently of the usual antibody-driven mechanisms of apoptosis, such as antigen-dependent cellular cytoxicity (ADCC).[31] When combined with intensive induction chemotherapy, GO has recently been shown to improve overall survival in older AML patients in a study from the UK[44] and in patients up to 70 years of age in a study from the Acute Leukemia French Association (ALFA).[45]

In this large randomized and double-blinded study, the monoclonal anti-CD33 antibody lintuzumab did not improve survival when added to LD cytarabine, with an estimated median survival in both treatment arms of approximately five months. The treatment arms were balanced for demographic and prognostic factors, as well as for total duration of drug exposure. Analysis of overall survival with respect to demographic and prognostic factors did not identify a subgroup of patients deriving benefit from lintuzumab treatment. Although response was not formally assessed in this study, in order to minimize the Quality of Life burden of bone marrow biopsies in patients receiving non-curative therapy, there was no difference in clinical benefit (as measured by peripheral blast clearance, hematology values and transfusion requirements) between the treatment arms.

Lintuzumab in combination with LD cytarabine was generally well tolerated. Infusion-related reactions, predominantly Grades 1-2 were more common in the lintuzumab treatment arm (51% lintuzumab *vs.* 7% placebo). No other clinically significant difference in patient safety between treatment arms was noted. Although 99% of patients were hospitalized at least once, only 16% of hospitalizations were due to adverse events. The high hospitalization rate, observed with a comparable rate in both treatment arms, likely reflects differences in local standards of care (e.g. admission for chemotherapy administration or blood transfusions) worldwide.

There are several possible explanations for the lack of clinical effect induced by lintuzumab in this study. Although the percentage of leukemic blasts expressing CD33 was similar between both treatment arms, the baseline blast percentage was higher in the lintuzumab arm, potentially resulting in disparate saturation of leukemic blasts between treatment arms. Similarly, a high CD33 antigen load in the peripheral blood could cause peripheral consumption of circulating antibody, subsequently decreasing its overall clinical effect.[46] However, repeated dosing of lintuzumab, as performed in this study, would likely overcome any undersaturation effect. Another possible explanation for the lack of clinical effect is that downregulation or internalization of CD33 upon antibody binding could protect leukemic cells from effector cell-mediated ADCC.[28] Along the same lines, recent research has demonstrated that NK-cell function may be greatly reduced in both MDS and AML, thereby potentially hampering ADCC effect.[47] Such findings may indicate a role

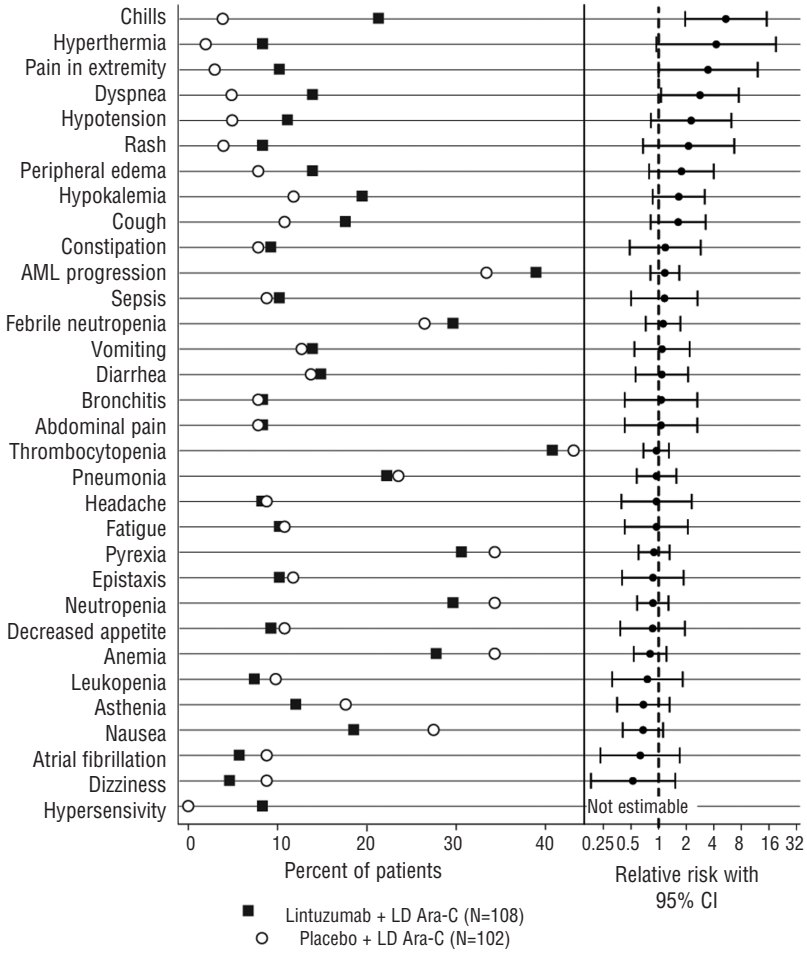

Figure 4. Relative risk of most common adverse events. For each adverse event, the incidence is displayed on the left and the relative risk is displayed on the right. Relative risk over 1 favors placebo + LD Ara-C and relative risk below 1 favors lintuzumab + LD Ara-C.

for the combination of lintuzumab with agents that could up-regulate effector cells and restore ADCC. Finally, a lack of CD33 expression among subpopulations of AML blasts could abrogate any significant effect on the natural history of the disease. As with conventional therapy, it is likely that resistance to lintuzumab, even within putatively susceptible CD33-positive cell populations, is mediated by multiple and heterogeneous mechanisms, many of which have yet to be defined.

Despite a negative outcome, the conduct and results of this study were instructive. As the largest completed study to date testing LD cytarabine in older patients with AML, survival in this trial was consistent with that of patients treated with LD cytarabine in the MRC AML14 trial,[21] with approximately one-quarter of patients surviving at one year. These results support LD cytarabine as a valid comparator for trials of non-intensive therapies in older AML patients, regardless of cytogenetic profile or history of previous hematologic disorder.

This trial also demonstrated that bone marrow assessments are not necessarily a requisite component for large studies in older adults with AML. Although survival and CRs have been correlated,[21] an increase in CR rate without a corresponding improvement in survival was also recently reported.[26] Moreover, recent data with azacitidine in higher-risk MDS and oligoblastic AML patients indicate that a response short of a CR can correlate with improved overall survival.[47] Bone marrow sampling may be less likely to guide treatment choices in patients undergoing low intensity therapy, intended to be delivered chronically and with lower expectations of CR, and no expectation of cure. Avoidance of bone marrow assessments in the current study was consistent with the treatment goals of patients in this population, which often focus upon Quality of Life. In summary, the addition of lintuzumab to LD cytarabine did not lengthen survival or induce clinical benefit in elderly patients with previously untreated CD33-positive AML. Low-dose cytarabine is an acceptable comparator therapy for trials of LD, non-curative approaches in older AML patients, regardless of cytogenetic profile. Despite its lack of clinical activity in this setting, monoclonal antibody therapy directed against CD33 remains a potentially useful strategy, given both the frequency of expression on myeloblasts and the saturability of this target. Future efforts toward the development of lintuzumab or other CD33 monoclonal antibodies will likely depend upon the ability to identify underlying molecular mechanisms that predict response and augment effector cell-mediated killing mechanisms.

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