

# 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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## Online Supplementary Appendix

### Design and Methods

#### Statistical analysis

Data were analyzed by Seattle Genetics, Inc., and all authors had access to the clinical trial data. The sample size for this Phase 2b screening trial was calculated using the method of Fleming and Richardson.<sup>1</sup> Reliable estimation of efficacy may be achieved with a phase IIb screening trial with one-fourth to one-third of the number of events required for a phase III trial evaluating the same primary efficacy endpoint. A total of 186 events (one-fourth of the number of events need for an a level of 0.001 and 90% power) were needed for this phase IIb screening trial. This number of events could be obtained by enrolling 105 patients per treatment arm (back calculated using a 2-sided  $\alpha$  of 0.31). A patient accrual period of 17 months and follow-up of at least 12 months (29 months total) and an 8-week treatment-associated increase in median survival (from 5 to 7 months, exponential parameters of 0.1386 and 0.0990, respectively, or hazard ratio of 0.714) were assumed. The sample size of 186 events provided approximately a 15% probability of observing a hazard ratio  $\leq 0.86$  if the assumed treatment effect existed (i.e., 8 week survival benefit with lintuzumab; median survival of 5 vs. 7 months). If the observed hazard ratio was  $>0.86$ , lintuzumab treatment would be considered unlikely to be effective.

All prospective efficacy analyses were conducted on the intent-to-treat (ITT) population, which included all randomized patients; patients were analyzed based on randomization assignment regardless of the treatment actually received. The primary efficacy analysis of OS included all source-verified deaths in the database at the time of database lock. Treatment difference in OS was evaluated using an unstratified log-rank test. The hazard ratio was estimated using a Cox model with treatment arm as the only covariate. The median survival time for each treatment arm was estimated using the Kaplan-Meier method. In the event of a statistically signifi-

cant result for the analysis of the primary endpoint (based on log-rank test) at a significance level of 0.31, analyses were to be performed on the secondary efficacy endpoints, using the Bonferroni gatekeeping procedure<sup>2,3</sup> to adjust for multiplicity and guarantee an overall  $\alpha$  level of 0.31.

All  $P$  values from inferential tests were 2-sided. Subgroup analyses were performed using hazard ratios and corresponding 95% confidence intervals. No formal interim analyses of efficacy were conducted.

The safety population included all randomized patients who received at least one dose of study drug; patients in the safety population were analyzed based on the treatment actually received. Patients who received any amount of lintuzumab were counted in the lintuzumab arm. Adverse events were tabulated using the Medical Dictionary for Regulatory Activities, version 13.0. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Potential differences between treatment arms in patient characteristics were evaluated retrospectively using Fisher's exact test for categorical variables and the T-test for continuous variables.

#### References

1. Fleming TR, Richardson BA. Some design issues in trials of microbicides for the prevention of HIV infection. *J Infect Dis.* 2004;190(4):666-74.
2. Dmitrienko A, Molenberghs G, Chuang-Stein C, Offen W. Gatekeeping Procedures Based on Marginal p-Values. In: *Analysis of clinical trials using SAS®: A practical guide.* SAS Institute Inc. Cary, N.C. 2005:108-12.
3. Marcus R, Eric P, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika.* 1976;63(3):655-60.

Online Supplementary Table 1.

Section/Topic	Item n.	Checklist item	Information for study registered with clinicaltrials.gov as NCT00528333
<b>Title and abstract</b>			
	1a	Identification as a randomized trial in the title	(Page 1) Randomized, phase IIb study of low-dose cytarabine and lintuzumab vs. low-dose cytarabine and - placebo in older adults with untreated acute myeloid leukemia (Abstract, page 2)
	1b	Structured summary of trial design, methods, results, and conclusions	
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	(Background, page 4) <ul style="list-style-type: none"> <li>◦ Improving outcomes in older adults with AML remains a formidable challenge.</li> <li>◦ The benefit of intensive chemotherapy in older adults is not clear-cut.</li> <li>◦ Low-dose cytarabine can be considered an appropriate control for clinical studies of new investigational agents. (Rationale, page 5):</li> <li>◦ CD33 is an attractive therapeutic target for AML because it is expressed on the majority of myeloblasts.</li> <li>◦ Lintuzumab (SGN-33) is a humanized monoclonal antibody directed against CD33.</li> <li>◦ In an earlier clinical study, lintuzumab demonstrated tolerability with modest monotherapy activity.</li> </ul>
	2b	Specific objectives or hypotheses	(Page 5) 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.
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	(Page 6) This was an international, phase IIb, parallel, randomized, double-blinded, placebo-controlled trial. 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.
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable. The protocol was amended once. The amendment included minor clarifications to methods, but no substantial changes.
Participants	4a	Eligibility criteria for participants	See description of eligibility criteria on page 6.
	4b	Settings and locations where the data were collected	(Page 9) 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.
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	(Page 7) 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) on Days 1-10. For Cycle 1 only, patients received study drug (lintuzumab 600 mg or placebo) intravenously (iv) once weekly (Days 1, 8, 15, and 22). For all subsequent cycles, patients received lintuzumab or placebo iv once every other week (Days 1 and 15).
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	(Page 7) <ul style="list-style-type: none"> <li>◦ 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.</li> <li>◦ Secondary end points were platelet and RBC transfusion requirements, infections/fevers requiring hospitalization or iv antibiotics, and serial peripheral blood counts. In addition, Quality of Life was assessed using the Functional Assessment of Cancer Therapy, Leukemia (FACT-Leu). In addition, protocol-defined clinical benefit (i.e. no peripheral blasts, ANC &gt;1.0x10<sup>9</sup>/L, platelets &gt;100x10<sup>9</sup>/L, and no transfusions for one week) was evaluated.</li> <li>◦ Secondary end points were analyzed weekly during Cycle 1 and every other week during subsequent treatment cycles. Pre-specified time points for evaluation of survival were 1, 3, 6, 9,</li> </ul>

	6b	Any changes to trial outcomes after the trial commenced, with reasons	12, 15, and 18 months. Secondary end point analyses for rates of infections or fevers requiring iv antibiotics or hospitalizations and rates of transfusions were up-dated to focus on the treatment period only as patients were not followed as frequently during survival follow up.
Sample size	7a	How sample size was determined	(Page 8) The sample size for this phase IIb screening trial was calculated using the method of Fleming and Richardson.
	7b	When applicable, explanation of any interim analyses and guidelines for interrupting treatment ('stopping rules')	(Page 7) An independent data monitoring committee (IDMC), including oncologists and a statistician experienced in clinical trials, monitored patient safety on an ongoing basis according to a formal charter. - No formal interim analyses of efficacy were planned or conducted, thus stopping rules were not developed.
Randomization: Sequence generation	8a	Method used to generate the random allocation sequence	(Page 6) 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).
	8b	Type of randomization; details of any restriction (such as blocking and block size)	(Page 7) The stratified randomization (block size = 4) was performed by Datatrak.
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	(Page 7) The stratified randomization (block size = 4) was performed by Datatrak.
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Datatrak generated the random allocation sequence and assigned participants to interventions. Centers enrolled patients.
Blinding	11a	If done, who was blinded after assignment to interventions (e.g. participants, care providers, those assessing outcomes) and how	(Page 6) This was a double-blind study. Participants, care providers, and those assessing outcomes were blinded, as an identical placebo control was used.
	11b	If relevant, description of the similarity of interventions	(Page 7) Study drug (lintuzumab or placebo) was administered iv on the same schedule. All patients received low-dose cytarabine on the same schedule.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	(Page 9) Treatment difference in OS was evaluated using an unstratified log rank test. The hazard ratio was estimated using a Cox's model with treatment arm as the only covariate. The median survival time for each treatment arm was estimated using the Kaplan-Meier method. In the event of a statistically significant result for the analysis of the primary end point (based on log rank test) at a significance level of 0.31, analyses were to be performed on the secondary efficacy end points, using Bonferroni's gatekeeping procedure to adjust for multiplicity and guarantee an overall alpha level of 0.31.
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	(Page 9) Subgroup comparisons were performed using hazard ratios and 95% confidence intervals.
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	(Page 30) CONSORT diagram is provided in Figure 1.
	13b	For each group, losses and exclusions after randomization, together with reasons	(Page 30) CONSORT diagram is provided in Figure 1.
Recruitment	14a	Dates defining the periods of recruitment and follow up	(Page 9) Data for this study were collected from November 2007 to August 2010.
	14b	Why the trial ended or was stopped	(Page 8) A total of 186 events were needed for this phase IIb screening trial. (Page 11) At the time of study termination, 187 patients (89%) had died.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	(Page 26) Baseline characteristics are provided in Table 1.
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	(Page 9) All prospective efficacy analyses were conducted on the intent-to-treat (ITT) population (N=211), which included all randomized patients; patients were analyzed based on randomization assignment regardless of the treatment actually received. ° The safety population (N=210) included all randomized patients who received at least one dose of study drug; patients in the safety population were analyzed based on the treatment actually received.

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	° (Details appear in a footnote to Table 2 on page 28). 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. (See description of efficacy results from the randomized trial on pages 11-12)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	(See description of efficacy results from the randomized trial on pages 11-12)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	(Page 5) As this represents the largest reported prospective experience of older AML patients treated with LD cytarabine, exploratory pooled and subgroup analyses are presented. (Results are provided on pages 14-15)
Harmful effects	19	All important harmful or unintended effects in each group (for specific guidance see CONSORT for harmful effects)	(Pages 12-14) Adverse events are described according to treatment arm. (Page 28) Table 2 provides the most common adverse events $\geq$ Grade 3. (Page 33) Figure 4 provides the relative risk of most common adverse events.
Discussion Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	(See discussion on pages 15-17)
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	(See discussion on pages 15-17)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	(See discussion on pages 15-17)
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	(Page 3, at end of abstract) <i>clinicaltrials.gov identifier: NCT00528333</i>
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	(Page 1) This work was supported by Seattle Genetics, Inc. (Page 8) 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.