Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research, FDA

ODAC Briefing Document: NDA 21-874, Genasense, G3139, Oblimersen
Genta Protocol GL303
Genta, Inc.

ODAC Meeting September 6, 2006

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Abbreviations used in this document

AE	Adverse Event (CTCAE criteria)
CLL	Chronic Lymphocytic Leukemia
CR	Complete response (NCI-WG-CLL 1996 criteria)
Cy	cyclophosphamide
Flu	Fludarabine
LDH	Lactate dehydrogenase
NSD	not significantly different
nPR	"nodular" PR (NCI-WG-1996 criteria, residual marrow lymphs)
ORR	Overall response rate (CR + nPR + PR)
PR	Partial response (NCI-WG-CLL 1996 criteria)
TTP	Time to tumor progression

A. Background

1. Proposed indication

"Genasense in combination with fludarabine and cyclophosphamide is indicated for the treatment of patients with chronic lymphocytic leukemia who are refractory to or have relapsed after therapy with fludarabine"

2. Background on Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL), the most common form of adult leukemia in the U.S., includes a broad spectrum of disease behaviors from an indolent process never requiring therapy to one of a persisting and progressive disease which may exhaust all available therapies. The median age at diagnosis is 72 years. In at least 95% of patients, the malignancy is a clonal expansion of B-lymphocytes resulting in myelo- and immuno-suppression as progressive accumulation of these cells occurs in blood, bone marrow, and lymphatic tissues.
Two staging systems, known as the Rai and the Binet systems have been published. Both characterize an increasing disease burden and provide prognostic information. The two systems have been combined to reflect outcomes more distinctly, and patients may be grouped into low risk, intermediate risk, and high risk groups.

Response categories

An NCI working group first proposed consensus criteria for assessing CLL in 1988.[1] In 1996, a revised set of criteria[2] were proposed for the diagnosis and assessment of response (and progression), based on a consensus of clinical disease experts (but not prospectively validated). Assessments were based on physical examination, blood counts, and bone marrow involvement. CT scanning was not required but if performed, should have been repeated later to assess response. Patients were grouped into 3 response categories:

a. CR, indicating complete resolution of disease, including resolution of symptoms, return to normal blood counts, and normal bone marrow aspirate and biopsy (no lymphoid nodules and less than 30% lymphocytes among the marrow nucleated cells)
b. nPR, indicating patients who fulfill all CR criteria except for the persistence of marrow lymphoid nodules (best seen on biopsy)
c. PR, indicating 50% or greater reduction in lymphocyte count, lymph node size, liver/spleen enlargement and some improvement in normal blood cell counts

(See appendix for further details.)

The outcomes of achieving each level of response are not well-established. The 1996 guideline separated the nPR category from CR as well as from PR, referring to a 1992 report by Robertson et al[3] from MD Anderson in which the prognostic features of 159 CLL patients receiving fludarabine (Flu) treatment were described. In that report, all responding patients had bone marrow biopsies and were classified as CR or PR or "nCR" status (nCR term later changed to nPR in the 1996 criteria). nCR denoted patients who clinically appeared to be in CR but had residual marrow lymphocytes in either a nodular or infiltrative (interstitial) pattern. Patients in the nCR group had a shorter time to progression (TTP) although similar overall survival (OS).[3]

Robertson et al [3] 1992 – time-to-progression was shorter for the nCR (nPR) patients, in this responder analysis

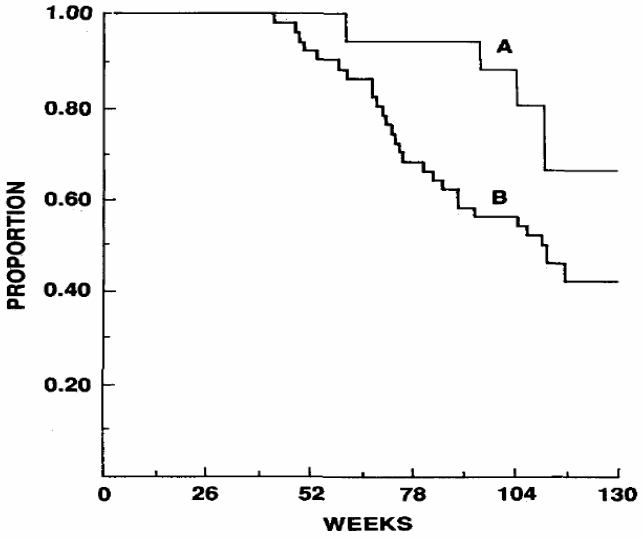


Fig 2. Time to progression for patients with CR and nCR. (A) CR: total 19, fail 5; (B) nCR: total 47, fail 28; $P < .03$.

A = CR

B = nCR

Robertson et al [3] 1992 – overall survival appeared similar for the CR and nCR patients in this responder analysis

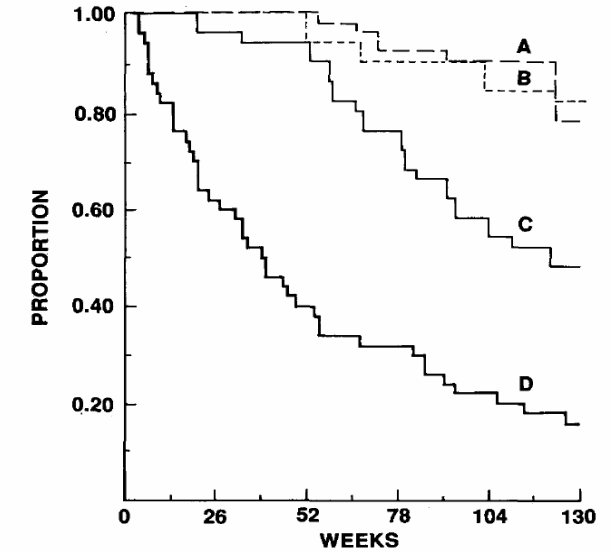


Fig 3. Overall survival for patients with CR, nCR, PR, and no response. (A) CR: total 19, four failures; (B) nCR: total 47, 10 failures; (C) PR: total 29, 15 failures; (D) no response: total 64, 53 failures; $P < .001$.

A = CR

B = nCR

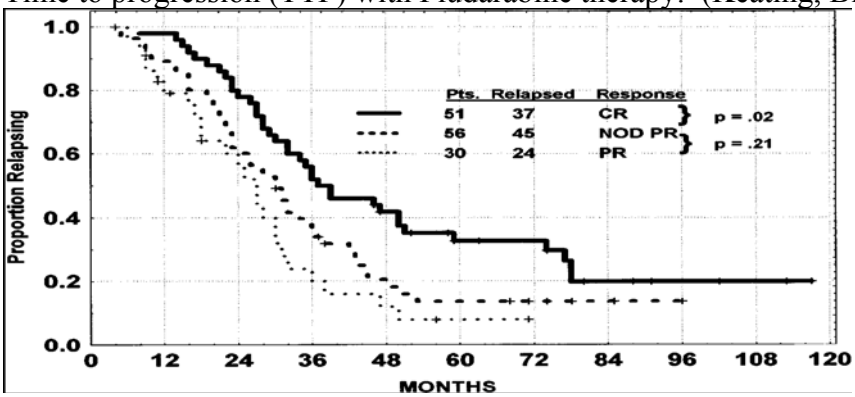
C = PR

D = no response

In general, increased treatment intensity is required to increase the rate and "depth" of CR, and this increased intensity is associated with increased treatment-related toxicity, particularly myelosuppression and immunosuppression. In the study now under NDA review, GL303, Genta chose to combine the CR and nPR responding patients for the primary analysis of efficacy. The overall response rate, composed of the CR, nPR and PR responders, was a secondary endpoint. Thus these endpoints will be examined further.

In 1998, Keating et al[4] reported a favorable survival outcome for CLL patients who achieved nod-PR (nPR) status, similar to the survival of those attaining a CR, using a retrospective responder analysis.

Time to progression (TTP) with Fludarabine therapy: (Keating, Blood 1998)



The median time to progression for all responders (CR, nod-PR, and PR) was 31 months. For the nod-PR patients, TTP was significantly inferior to the TTP for the CR patients but not significantly different than for PR patients.

In 2003, Keating reported that "even as late as 1986, persistent nodules in the bone marrow biopsy were allowed for patients to be classified as complete remissions. It is now obvious that the persistence of these nodules is associated with persistence of CLL with a higher propensity for relapse."[5]

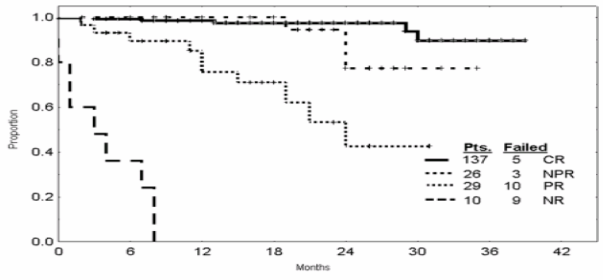


Figure 5. Time-to-treatment failure of 202 chronic lymphocytic leukemia (CLL) patients treated with fludarabine, cyclophosphamide, and rituximab (FCR) as initial therapy according to response (NCIWG criteria).

Abbreviations: CR, complete response; PR, partial response; NR, no response; NCIWG, National Cancer Institute Working Group.

Time-to-treatment-failure by response category: Keating, ASH Education Book, 2003 [5]

There remains uncertainty regarding the outcome after achieving a response fulfilling the nPR criteria. Most likely, patients achieving an nPR response have an outcome intermediate between the CR and PR groups. Also, it is usual to include PRs in assessing treatment responses. Patients who achieve a CR or nPR, by definition have resolution of their symptoms and signs of the disease process. Some who have only a PR also have reduction or resolution of some aspects of the disease process. While it is possible to look at the durations of response for each response category, there is considerable variability in the results. As CR rates improve, molecular remission status may become more informative. However, in reporting results of CLL therapy in the last decade, authors use overall response rates based on the 1996 criteria, which include CR, nPR, and PR groups. In relapsed acute leukemias, achievement of a CR with durability may support a full approval. In contrast to the general lack of benefit in achieving a PR in the acute leukemias, a PR can be clinically helpful for patients with CLL.

Several therapies are available for those CLL patients with progressive disease in need of treatment, although a survival advantage has never been demonstrated prospectively for a particular regimen. The alkylating agents chlorambucil and cyclophosphamide were approved for palliative treatment of CLL. Fludarabine (Flu) was approved in 1991, and alemtuzumab was approved in 2001. When considering treatment results, it is important to note that the studies supporting approval for Flu and alemtuzumab were conducted in previously treated patients, as was this Genta NDA study.

In 1991, Fludarabine (Fludara for injection, Berlex, now Schering AG) was approved "for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The safety and effectiveness of Fludarabine in previously untreated or non-refractory patients with CLL have not been established."

As described in the fludarabine label, two clinical studies were submitted and reviewed by FDA.

	N	CR	PR	ORR	Response duration - median	Survival for all pts - median
MD Anderson	48	13%	35%	48%	91 weeks	43 weeks
SWOG	31	13%	19%	32%	65 weeks	52 weeks

Response criteria, ORR (CR plus PR) used the NCI-WG 1988 criteria.
In this system, CR and PR are similar to the revised criteria of 1996.

Patients in these studies were refractory to alkylating agents. Response rates were expressed as overall response (ORR), combining the CR and PR patients. Also, in the combined studies, the mean hemoglobin increased from 9.0 to 11.8 g/dL in a subgroup of anemic pts independent of transfusion or erythropoietin, and the mean platelet count improved from 63,000 to 103,000/mm^3.

In 2001, alemtuzumab (Campath, Millennium and Ilex partners) received accelerated approval "for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been

treated with alkylating agents and who have failed fludarabine therapy. (Determination of the effectiveness of Campath is based on overall response rates. Comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted.)" Alemtuzumab is a humanized monoclonal antibody directed against CD52, a lymphocyte cell surface protein antigen.

Three studies were submitted and reviewed for the alemtuzumab approval. In all of the studies, patients had a median of 3 prior therapies. In the first study of 93 pts, all were previously treated with alkylating agents and had failed fludarabine. Fludarabine (Flu) failure was defined as progressive disease on Flu or failure to achieve a CR or PR on Flu, or relapse within 6 months of last dose of Flu. In the Flu refractory group, alemtuzumab had a 33% response rate with clearing of peripheral blood and bone marrow. Response criteria were based on the NCI-WG 1996 guideline consisting of CR and PR groups.

Three clinical studies submitted and reviewed in the alemtuzumab label

	N	Prior therapy AA	Flu	CR	PR	ORR	Response Duration median	PFS (months)
Study 1	93	100%	100% **	2%	31%	33%	7 mo	4
Study 2	32	100%	34%	0%	21%	21%	7 mo	5
Study 3	24	92%	100%	0%	29%	29%	11 mo	7

AA, alkylating agent; Flu, fludarabine; PFS, progression-free survival
** All were Flu refractory

In this NDA study, GL303, the control group received a standard combination regimen of Flu plus cyclophosphamide (Cy). The effects of this combination (Flu/Cy) were reported in 2001 by O'Brien et al[6] describing the MD Anderson experience in 128 CLL patients who had received prior therapy, as well as a group who were previously untreated. Most patients received Flu 30 mg/m2 daily times 3 days plus Cy 300 mg/m2 daily times 3 days together every 4-5 weeks.

MD Anderson results with the Flu/Cy combination [6]

Prior Therapy with:	No. of Patients	CR (%)	Nodular PR (%)	PR (%)	Overall Response (%)
1. None	34	35	29	24	88
2. Alkylating agents	20	15	25	45	85
3. Alkylating agent + fludarabine [a]	46	12	17	51	80
4. Alkylating agent + fludarabine [b]	28	3	13	26	39 (sic) (? 42%)

a: Sensitive to last treatment = responded then later relapsed
b: Refractory to last treatment = progressed on or failed to respond to last therapy with Flu (and 62% of these also were judged refractory to alkylating agents)

In this O'Brien study, responses were expressed in terms of CR, nPR, and PR. In the 46 patients judged to be Flu sensitive, the CR rate was 12%, the nPR rate was 17%, the PR rate was 51%, and the overall response rate (ORR) was 80%. Among 28 patients judged to be Flu refractory, the ORR was 39% (or 42%; the discrepancy is not addressed in the paper).

3. Background on Genasense

Genasense is a nucleotide polymer synthesized to bind specifically to the messenger RNA coding for the synthesis of the Bcl-2 protein. Binding leads to destruction of the m-RNA selectively, leading to a reduction in Bcl-2 protein in cells. Bcl-2 expression is reported to be upregulated in many tumor types, including CLL, and is thought to be important for the maintenance of cancer cell viability (anti-apoptotic) and to contribute to chemo- and radiotherapy resistance. Because drug levels drop rapidly when IV administration is stopped, Genasense has to be administered by a continuous IV infusion over several days per month, requiring a central venous access line and portable pump.

Clinical studies with IV Genasense began in 1995. A phase 3 trial comparing DTIC alone with Genasense plus DTIC was the subject of an NDA and ODAC meeting in 2004. The trial failed to achieve its primary endpoint of improved overall survival with the addition of Genasense. Progression-free survival was not substantially improved, and response rates were low on both the combination arm (11.7%) and the DTIC alone arm (6.8%). The ODAC voted to recommend not approving the application, and Genta withdrew the NDA.

Because Genasense requires continuous IV infusion via a pump, catheter-related inconvenience and complications can occur.

4. Regulatory background

In study GL303, Genta proposed to compare the response rate as defined by the sum of CR plus nPR responders for the primary endpoint. At an end-of-phase 2 meeting and a special protocol assessment meeting in 2002, FDA did not agree with the choice of this endpoint for the primary analysis. FDA suggested then that a time-to-progression comparison of the two study arms would be more informative. FDA did accept the proposed statistical analysis plan in 2004.

Genta has submitted a protocol (GL305) for a special protocol assessment for evaluation of Genasense plus chemotherapy in patients with CLL not previously treated. FDA did not reach agreement with Genta or "approve" the protocol.

5. Issues for ODAC to consider in the context of study GL303

In some leukemia populations, FDA has accepted durable remissions as evidence of clinical benefit. The addition of Genasense to Flu plus Cy results in an improved response rate when the response rate is defined by the CR plus nPR patients, 16.8% versus 6.7% in the control arm. For the overall response category, CR plus nPR plus PR patients, there is no

improvement with the addition of Genasense. Furthermore, there is no apparent difference in overall survival or time to disease progression between the two study arms.

Given these results, does this single, open-label, randomized study fulfill the requirements that a single study should meet to demonstrate substantial evidence of effectiveness in the context of Genasense-related toxicity? Do the response findings in this population represent evidence of clinical benefit?

B. Study Design for GL303

(excerpted from protocol version 7 dated April 16, 2004 and elsewhere as noted)
GL303 was a prospective, open-label, randomized (1:1), two arm, multicenter, international study which began in August 2001. The last treatment was concluded in June 2003. The protocol was amended 6 times to version 7, dated 4/14/04.

1. Primary endpoint

The proportion of subjects who achieve a CR or nPR as judged by an independent blinded reviewer, using the NCI-WG response criteria (1996)

2. Secondary endpoints

- Overall response rate (CR + n-PR + PR)
- Survival
- Duration of Response
- Time to Disease Progression (TTP)
- "Clinical Benefits" defined as:
    - Resolution of B-symptoms (night sweats, fever)
    - Impaired mobility due to lymphadenopathy, impaired cosmesis, abdominal discomfort due to hepatosplenomegaly, early satiety,
    - Resolution or reduction in massive splenomegaly
    - Relative improvement in performance status
    - Improvement in disease-related anemia
    - Improvement in fatigue as measured by the Brief Fatigue Inventory (BFI)

3. Population

Major inclusion criteria:

- Patients with relapsed or refractory CLL who require therapy and have previously received fludarabine and are classified as:
    - Primary Resistance – (defined as progressive disease without response during administration of at least two cycles of myelosuppressive chemotherapy)

or

    - Relapsed Disease – (defined as having achieved a response and then relapsed [i.e., post remission or post plateau] on or off therapy)

- Measurable disease established by the NCI Working Group criteria for diagnosis of CLL (all of the following must be present):
    - Absolute lymphocytosis > 5000/mm^3
    - The lymphocytosis must consist of small to moderate size lymphocytes, with < 55% prolymphocytes, atypical lymphocytes, or lymphoblasts morphologically determined by manual differential
    - Bone marrow aspirate smear with > 30% of nucleated cells that are lymphoid or a bone marrow core biopsy that shows lymphoid infiltrates compatible with CLL
    - Normocellular or hypercellular bone marrow
    - Intermediate or high risk CLL (Modified Rai stage
    - Patients with intermediate risk disease must satisfy at least one of the criteria for active disease

Adequate baseline organ function
ECOG PS 0, 1, or 2

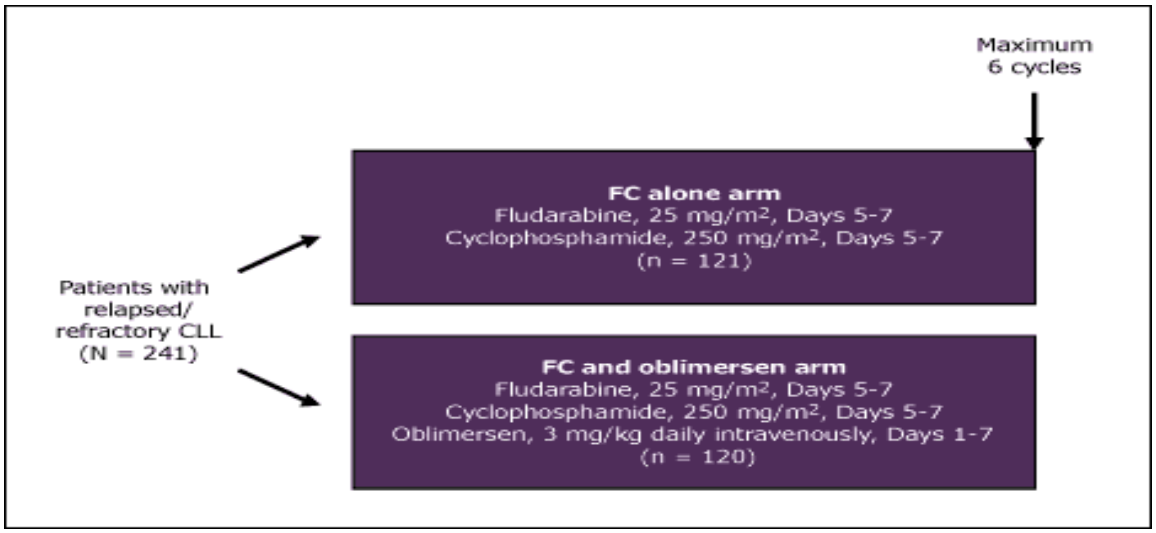
Major exclusion criteria:

- Advanced heart disease
- therapeutic anticoagulation
- prior stem cell or organ allograft

4. Treatment plan

Patients were centrally randomized after being stratified by 3 factors:

- Responsive to prior treatment with fludarabine versus refractory to prior fludarabine (defined as response lasting < 6 months)
- 1 or 2 prior treatment regimens versus 3 or more prior regimens
- Greater than 6-month response vs. response to last therapy ≤ 6 months



source: Genta, Inc.

Genasense was administered via a central venous catheter by continuous infusion for one week of each monthly cycle. Up to 6 cycles were planned for patients tolerating therapy and not progressing. Appropriate dose modifications for Flu and Cy were provided.

All patients also were required to receive supportive therapy including:

- G-CSF (filgrastim) 5 ug/kg/d for at least 1 week of each cycle
- Acyclovir 400 mg 3 times daily on therapy and for 6 months after
- Trimethoprim-sulfamethoxazole DS twice daily three times weekly on therapy and for 6 months after
- anti-emetics (5-HT_3 blockers)
- Allopurinol 300 mg daily for at least the first 2 weeks of cycle 1
- All blood products to be transfused should be irradiated (GVH observed with Flu)

5. Efficacy and safety assessments

Response was assessed after every cycle while on therapy, then every 2 months, along with symptom assessments, physical exams, transfusion history, blood counts, and repeat imaging if a determinant of response. Adverse events (AEs) were assessed and graded according to NCI Common Toxicity Criteria (CTC) version 2. All data was recorded on case report forms.

6. Statistical issues

The sample size of 200 patients was determined to provide a power of 80% with an overall alpha (two-sided) of 0.05, based on the following assumptions:

- The response rate (CR + n-PR) for subjects who received Flu/Cy alone will be 24%
- Addition of G3139 will increase response to a total rate of 44% (absolute increase 20%)
- Patients will be allocated equally to Flu/Cy and to Flu/Cy + G3139

The primary analysis was performed on the CR plus nPR response population as determined by independent, blinded review (Dr. Kanti Rai) of the ITT population (all randomized).

Protocol version 7 did not include a plan of analysis addressing multiplicity of secondary analyses, but did provide the following list of secondary variables:

"13.1.2 Secondary efficacy variables include:

- Overall response rate (CR + n-PR + PR)
- Survival
- Duration of Response
- Time to Disease Progression (TTP)
- Clinical Benefit defined as:
- Resolution of B-symptoms (impaired mobility due to lymphadenopathy, impaired cosmesis, abdominal discomfort due to hepatosplenomegaly, early satiety, night sweats, fever)
- Resolution or reduction in massive splenomegaly
- Relative improvement in performance status

- Improvement in disease-related anemia
- Improvement in fatigue as measured by the Brief Fatigue Inventory (BFI)"

In a statistical analysis plan updated August 3, 2004 (pages 11-12) a plan to account for multiplicity was proposed by specifying a sequence of analyzing secondary endpoints:
"To guard against spurious inflation of the Type I error rate, secondary efficacy endpoints are classified into two categories and a stepwise analysis is proposed within each category. Category I includes overall response rate, time to progression, survival time, and duration of response. Category II includes all clinical benefit endpoints.
Within Category I, the analyses of efficacy endpoints will be conducted for the ITT population in a stepwise manner to control a family-wise error rate of 0.05 following the order of:
1. Time to progression
2. Overall response rate
Duration of response will be analyzed descriptively only. Survival time will be analyzed with a later cut-off date (on or prior to 30 June 2006) when all subjects have had an opportunity for a 3- year follow-up from randomization
Each of the above endpoints will be tested at α=0.05 level. If significance is achieved, the test of the next endpoint will be performed. If not, confirmatory conclusions on subsequent endpoints will not be drawn."

"Similarly, analysis of clinical benefit endpoints in Category II will also be conducted in a stepwise manner to control a family- wise error rate of 0.05. The primary analysis of each clinical benefit endpoint will be performed sequentially in the order of:
1. Resolution of B-symptoms
2. Resolution or reduction in massive splenomegaly
3. Improvement in disease-related anemia
4. Decrease in RBC transfusions
5. Decrease in erythropoietin administration
6. Improvement in ECOG performance status
Disease-related symptoms other than B-symptoms, improvement in fatigue (both as measured by BFI and as measured by resolution of the pre-existing condition) will be analyzed descriptively only."

FDA has chosen to examine all the protocol-specified secondary endpoints for this review.

C. Results of GL303

First patient enrolled:	August 13, 2001
Last patient completed therapy:	June 2003
Data cutoff for NDA report:	June 17, 2005
NDA submitted:	December 28, 2005

1. Demographics and disease characteristics

The two treatment arms appear reasonably well-balanced for baseline characteristics including:

- age (median 62 years, ~75% male)

- performance status (PS 0 in about 33%; PS ≥ 1 in about 66%)
- disease stage (Rai stage 1-2 and Rai stage 3-4 each ~ 50%)
- presence of baseline disease-related symptoms
- baseline hemoglobin level, platelet counts, cytogenetics, beta-2 microglobulin, and proportion with elevated LDH
- mean absolute lymphocyte count (79,000/mm^3)
- proportions with lymphadenopathy, hepatomegaly, and splenomegaly
- prior therapy including
    - number of prior regimens (one or two, 50%; 3 or more, 50%)
    - exposure to Flu (100%) and to Cy or chlorambucil (70%)
    - proportion of patients considered non-refractory to Flu (70%)
    - duration of response to last therapy > 6 months (44%)

Prior Treatment History	FC and Genasense (n = 120)	FC Alone (n = 121)
Number of prior regimens	%	%
• 1-2	50	52
• ≥3	50	48
Fludarabine sensitivity		
• Relapsed (sensitive)	43	41
• Refractory	58	59
Response to last therapy		
• ≤6 mos	55	57
• > 6 mos	45	43
Prior alkylating agents		
Cyclophosphamide/ Chlorambucil	70	71
Other prior therapy		
• Vinca alkaloids	31	30
• Rituximab	28	28
• Alemtuzumab	6	7

source: Genta FDA Briefing document February 2006

2. Drug exposure

Five patients on the Genasense arm and 6 on the control arm did not initiate therapy. Thus, the safety population consisted of 115 patients who received therapy with Genasense plus Flu/Cy and 115 patients who received Flu/Cy. On each study arm, the planned doses of Flu and Cy were equivalent and given in similar 4 week intervals. The median number of treatment cycles completed was the same in each treatment group (4.0 cycles). The number of patients completing all 6 cycles was 30% (36/115) for the Genasense arm compared to 37% (45/115) for the Flu/Cy control arm. Through the planned 6 cycles, the mean and median doses of Flu and Cy were very similar in both study arms and within 10% of the planned dosing.

The planned dose of Genasense was 3 mg/kg/Day times 7 days (21 mg/kg). The mean and median G3139 dose per cycle (consisting of 7 days' infusion) was 19.5-20.5 mg/kg.

3. Efficacy

In total, 241 patients were randomized at 100 sites in 8 countries (G3139 plus Flu/Cy group, 120 subjects; Flu/Cy group, 121 subjects). A total of 230 (95.4%) subjects (115 subjects in each treatment group) initiated protocol therapy.

PRIMARY ENDPOINT

For the sponsor's primary endpoint, using the ITT population, the independent blinded reviewer determined the CR plus nPR response rate was 16.7% (20/120) for the Genasense plus Flu/Cy compared to 6.6% (8/121) for the Fly/Cy control arm. FDA examined the bone marrow slides and other data submitted and agrees with Genta's analysis, although several of the marrow samples did not include biopsies.

SPONSOR'S SECONDARY ENDPOINTS
(As listed in the Clinical Study Report GL303, November 25, 2005, pages 57-58)

1. Overall response rate – ORR (CR + n-PR + PR)
2. Time to Disease Progression (TTP)
3. Survival –overall (OS)
4. Duration of Response
5. Clinical Benefit as defined

1. Overall response rate (ORR):

FDA and Genta calculated the overall response rate (ORR). In GL303, ORR was slightly lower for the Genasense arm (41%) compared with the control arm (45%).

Response Efficacy analysis summary

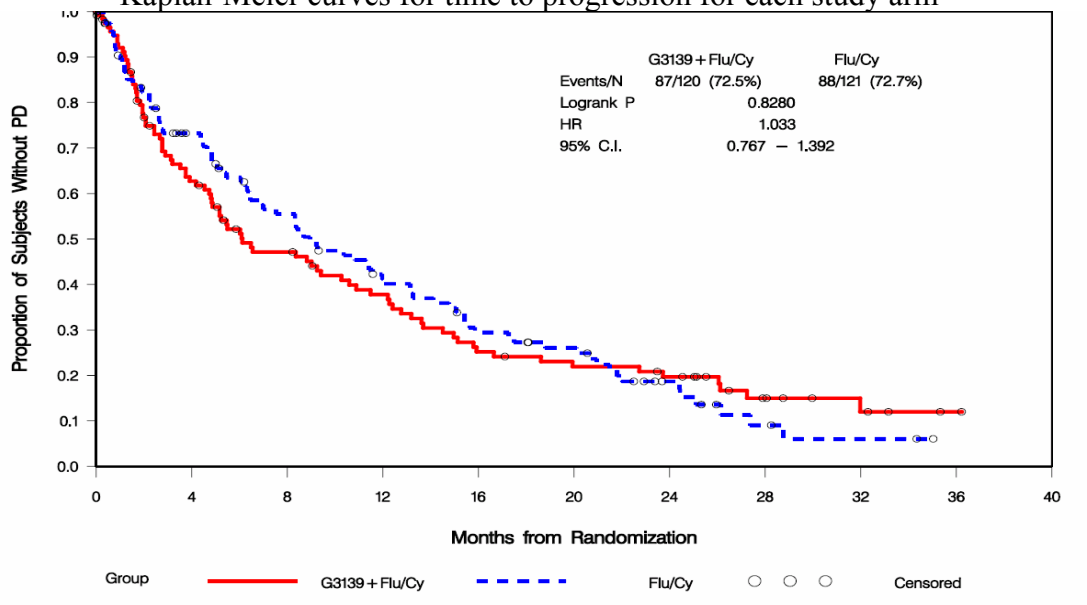
GL303 N= 241 Results	G3139 plus Flu/Cy (120) n (%)	Flu/Cy (121) n (%)	P value
CR	11	3	0.03 [a]
nPR	9	5	
CR + nPR [95% CI]	20 (16.7) [10.5, 24.6]	8 (6.6) [2.9, 12.6]	0.025 [b]
PR	29	46	
ORR: CR + nPR + PR	49 (41)	54 (45)	0.64 [b]

a. Fisher exact test

b. Pearson Chi-square test, continuity corrected

2. Time to progression (TTP):

Kaplan-Meier curves for time to progression for each study arm

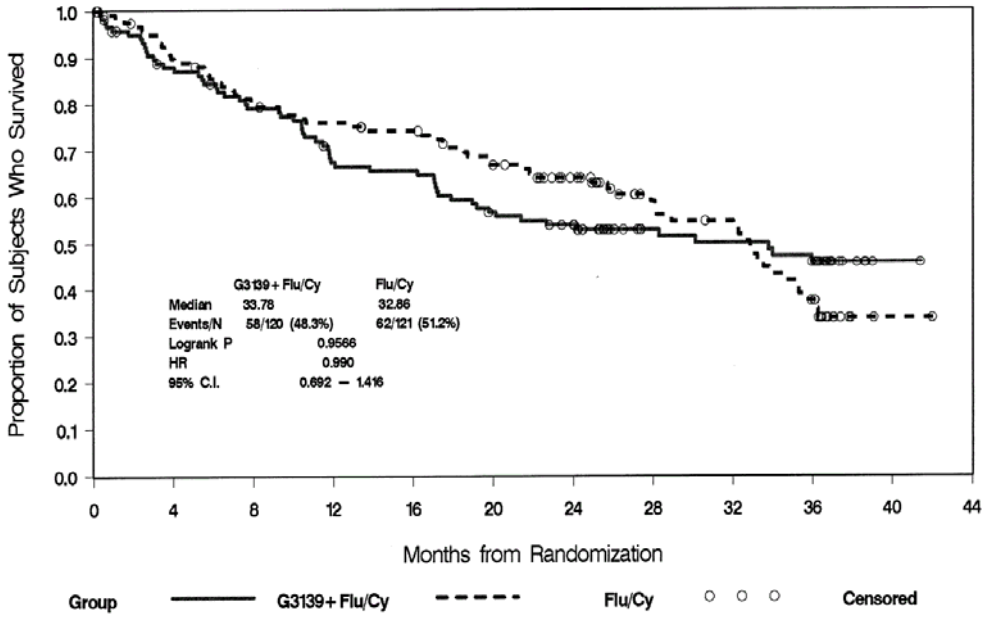


Time to progression reflects the treatment effect on the entire group of patients in each study arm. In each group, 27% were censored. For TTP, no difference was demonstrated between the two treatment arms (logrank p = 0.83; hazard ratio = 1.03). The median TTP for the Genasense arm is 6 months compared with 9 months for the control arm.

3. Overall survival:

The protocol-specified analysis was to be performed in June 2006 after all patients had completed at least three years off therapy.

Figure 14.2.4.2
Kaplan–Meier Curves of Survival Time
Intent–to–Treat Population

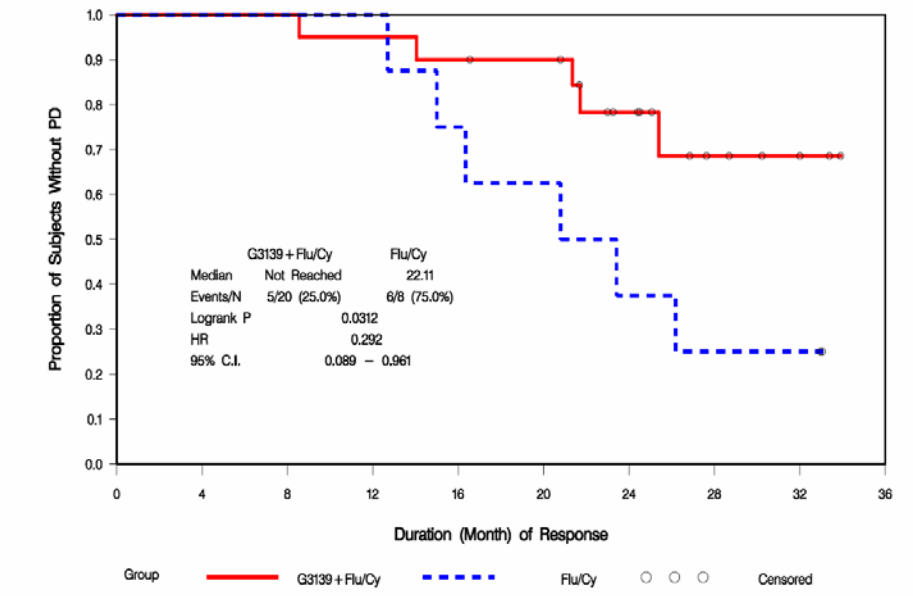


For overall survival, no difference was demonstrated between the two groups (logrank p =0.96; hazard ratio = 0.99). The median OS for the Genasense arm is 34 months versus 33 months on the control arm. For the control arm, 49% of patients were censored. for the Genasense arm, 52% of patients were censored.

4. Duration of response:

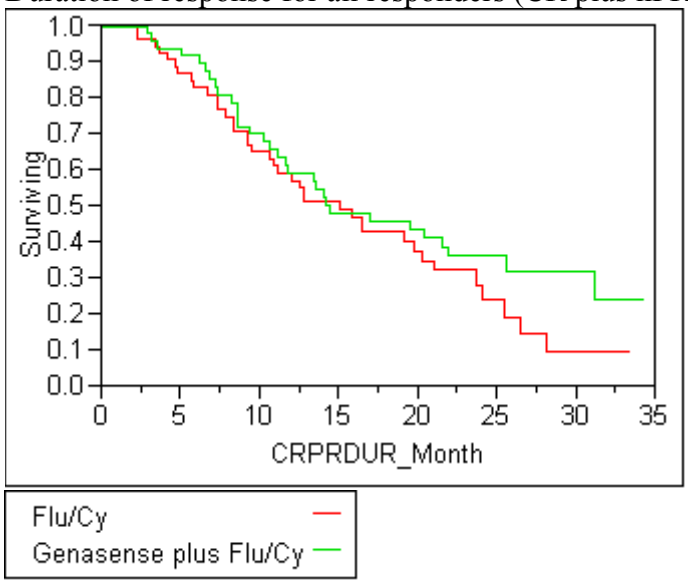
The applicant provided a Kaplan-Meier graph of duration of response, only for the CR and nPR patients, showing that the median duration was 22 months for the Fly-Cy group (6 of 8 have progressed) and that the median has not been reached for the G3139 plus Flu-Cy group (5 of 20 have progressed). Genta pre-specified a duration-of-response analysis to be calculated for (CR + n-PR) subjects and also for (CR + nPR + PR) subjects (Statistical Analysis Plan: Protocol GL303 Release Date: 3 Aug 2004, page 8).

Genta provided results for the CR plus nPR group as shown here. This represents a responder-type of analysis.



For comparison, the FDA performed an analysis of duration of response for the CR plus nPR plus PR population (ORR).

Duration of response for all responders (CR plus nPR plus PR)



For all responders, there is no difference in durations between the two study groups. The median duration of response was 15.2 months for the control arm compared to 14.5 months for the Genasense arm.

5. Other secondary endpoints:

The applicant specified the analysis for other secondary endpoints variously during the 6 protocol revisions and subsequent statistical analysis plan (See appendix for further details). The protocol did not pre-specify the plan of analysis which Genta has provided for duration of symptom-free days; thus this may be considered exploratory. Genta has provided a description of the number of patients who were symptom-free for a period of 180 days and an analysis of "symptom-free time" based on the level of response. No justification for this choice of time interval, and no adjustment in consideration of multiplicity of analysis of other possible time intervals is provided. The analysis is invalid for making any inferences between the two treatment arms. However, the applicant's analysis showed that for patients achieving a PR, the mean and median symptom-free days were 397 and 349 days, respectively, confirming a utility to achieving PR status for these patients and the importance of including PR patients in efficacy analyses.

Genta also observes that "analyses of other 'clinical benefit endpoints' showed no statististically significantly different findings between treatment groups" (Clinical Study Report GL303, page 123, dated November 25, 2005).

The FDA analyzed each of the sponsor's pre-specified secondary endpoints. FDA is in agreement with Genta's observation that "analyses of other clinical benefit endpoints showed no statististically significantly different findings between treatment groups."

- Potential "clinical benefit endpoints" examined include:
    - Resolution of B-symptoms (night sweats, fever)
    - Impaired mobility due to lymphadenopathy, impaired cosmesis, abdominal discomfort due to hepatosplenomegaly, early satiety,
    - Resolution or reduction in massive splenomegaly
    - Relative improvement in performance status
    - Disease-related anemia:
        - more patients required red cell transfusions with Genasense (36% versus 29%)
        - more patients required platelet transfusions with Genasense (18% versus 5%)
    - Improvement in fatigue as measured by the Brief Fatigue Inventory (BFI)

The GL303 study failed to demonstrate any "clinical benefit" improvements for the addition of Genasense to Flu/Cy.

Genta has provided no evidence that this dose of Genasense in these patients alters Bcl-2 or that an alteration in Bcl-2 in these patients provides any benefit.

4. Safety

The following analyses were conducted and reported by Genta. FDA is in the process of evaluating these findings.

Genta table of treatment-emergent adverse events occurring in ≥ 15% of subjects: Safety Population

	All grades		**Grade 3**		**Grade 4**	
Preferred term	**GFC (N=115)** **%**	**FC (N=115)** **%**	**GFC (N=115)** **%**	**FC (N=115)** **%**	**GFC (N =115)** **%**	**FC (N=115)** **%**
At least 1 TEAE	100	97	50	44	29	21
Nausea	72	48	8	2	0	0
Thrombocytopenia	49	40	29	18	4	2
Fever	48	29	3.5	3	0	0
Fatigue	44	31	6	3	0	2
Anemia	39	42	11	10	3.5	5
Vomiting	30	23.5	5	1	1	0
Cough	28	22	1	0	0	0
Constipation	26	19	2	1	0	0
Neutropenia	24	33	12	13	7	11
Headache	23.5	14	1	3	0	0
Diarrhea	22	14	1	1	0	0
Dyspnea	21	16.5	4	2	1	0
Dehydration	17	2	1	1	0	0
Rigors	16.5	7	2	0	0	0
Weight decreased	16.5	5	1	0	0	0
Catheter-related complications	16	3	0	0	0	0

Adapted from Genta Table 14.3.1.3.2, GL303 CSR

The addition of Genasense adds to the toxicity of the chemotherapy, particularly for nausea, thrombocytopenia, fever, fatigue, headache, dyspnea, dehydration, rigors, and IV catheter-related complications. There were 3/115 Genasense infusion-related deaths in the first cycle in which patients never received the Flu/Cy treatment.

D. Conclusions

Genta has provided evidence that the response rate, defined as the proportion of CR plus nPR patients is statistically significantly greater with the addition of Genasense to Flu/Cy. However, this absolute difference of 10% as opposed to the 20% difference as designed is of questionable clinical significance.

Other analyses pre-specified by Genta show no differences between the two study arms for the following secondary endpoints:

- Overall response rate defined as CR plus nPR plus PR patients
- Overall survival
- Time to progression
- Duration of response for all responders (CR plus nPR plus PR)
- Symptom-free interval for all responders (CR plus nPR plus PR)
- Resolution of B symptoms
- Resolution or reduction of massive splenomegaly
- Improvement in ECOG performance status
- Disease-related anemia
- Use of red cell transfusions
- Changes in fatigue
- Resolution of other disease-related symptoms

Additional exploratory analyses by FDA noted no improvement with Genasense

- For patients judged by Genta as Flu refractory, either by CR + nPR or by ORR
- For patients with 3 or more prior treatments,
- For patients whose response to prior therapy was < 6 months
- For patients ≥ age 65
- For women
- For patients with baseline hemoglobin under 11 g/dL
- For patients with baseline platelet count below 100,000/mm3
- For patients with baseline elevated LDH (present in 43% overall)

The addition of Genasense to Flu/Cy appears to add to the toxicity of the treatment.

Appendix

FDA Effectiveness Guidance Document 1998 - A single trial must be well-conducted, internally consistent, and demonstrates a compelling result – statistically strong evidence of an important clinical benefit

- Characteristics of a single study to support effectiveness:
  - Large, multicenter study
    - no single site or investigator disproportionately responsible for result
  - Consistency across study subsets
    - consistency across key subsets, i.e. severity of disease, stage, age, etc
  - Multiple studies within the study
    - pairwise comparisons within the study are consistent
  - Multiple endpoints involving different events
    - somewhat unrelated endpts i.e. MI and death show consistent effect
  - Statistically very persuasive- very low p values

NCI-WG Response criteria 1996 as used in the GL303 protocol

"The clinical response criteria were adapted from the National Cancer Institute-sponsored Working Group guidelines. Bone marrow response assessment will be conducted by a blinded expert hematopathologist independent review. Clinical response assessment will be performed by external CLL expert review in a blinded fashion."

Complete response (CR): requires subjects to meet all of the following four clinical criteria for a period of at least 2 months:

1. Hematology:
   - Neutrophils: = 1,500 cells/μL
   - Platelets: = 100,000/μL
   - Lymphocytes: < 5,000 cells/μL
   - Hemoglobin: = 11.0 g/dL without transfusion
2. Lymph nodes:
   - Absence of CLL-related lymphadenopathy by physical examination and appropriate radiographic techniques.
3. Liver/spleen:
   - Normal size on physical examination
4. Constitutional symptoms:
   - Absence of fever and night sweats

In addition, a bone marrow aspirate or biopsy meeting standard response criteria is required to confirm clinical response.

Nodular partial response (n-PR): A nodular partial response (n-PR) is a CR by all criteria except for persistent lymphoid nodules in bone marrow.

Partial response (PR):
requires subjects to meet all of the following criteria for a period of at least 2 months:

- = 50% decrease in peripheral blood lymphocyte count from baseline
- = 50% reduction from baseline in lymphadenopathy (if present at baseline)
- = 50% reduction from baseline in the size of the liver (if abnormal at baseline)
- = 50% reduction from baseline in the size of the spleen (if abnormal at baseline)
- Maintenance of one or more of the following:
  - Neutrophils > 1,500/μL or 50% increase over baseline
  - Platelets > 100,000/μL or 50% increase over baseline
  - Hemoglobin >11.0 g/dL without transfusion

Progressive disease (PD):
is defined as meeting one or more of the following criteria:

- 50% increase in the sum of the products of at least two lymph nodes (at least one node must be 2 cm) or appearance of new disease-related lymph nodes.
- 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin or the appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- 50% increase from the nadir in peripheral blood lymphocytes to at least 5,000/μL.
- Transformation to a more aggressive histology (e.g., Richter's syndrome or prolymphocytic leukemia)

In the GL303 study, clinical benefit is to be measured by:
(Statistical Analysis Plan: Protocol GL303 Release Date: 3 Aug 2004)

1. Resolution of B-symptoms
B-symptoms consist of fever and night sweats in this study. Resolution of B-symptoms is defined as the absence of both B-symptoms (if present at baseline). The primary analysis of this endpoint will be performed among the subjects with B-symptom at baseline using the Pearson Chi-square test. Among all subjects, with respect to the status (presence or absence) of B-symptoms during study, the two treatment groups will be compared using the CMH Chi-Square test stratified by baseline status.
2. Resolution or reduction of massive splenomegaly
Massive splenomegaly is defined as the enlargement of the spleen to at least 6 centimeters (cm) below the costal margin on physical examination. Resolution of massive splenomegaly is the complete shrinkage to "normal," as defined by the examining physician. Reduction in massive splenomegaly is defined as at least a 50% reduction in measurement from baseline. The primary analysis of number (%) of subjects with resolution or reduction of massive splenomegaly will be performed among subjects with massive splenomegaly at baseline using a Pearson Chi-square test. Among all subjects, numbers (%) of subjects with a normal spleen or 50% reduction in

massive splenomegaly will be analyzed using the CMH Chi-Square test stratified by the baseline status (normal or abnormal).

3. Relative improvement in ECOG performance status

A subject will be counted as improved if the ECOG performance status score decreases from baseline by 1 or more. Among all subjects, numbers (%) of subjects who had an ECOG score of 0 or improved by at least one level will be summarized and compared between the two treatment groups using a CMH Chi-Square test stratified by the baseline
status (ECOG 0 or >0).

4. Improvement in disease-related anemia

The laboratory parameter serum hemoglobin will be analyzed for improvement in disease-related anemia. Disease-related anemia is defined as hemoglobin ≤ 11 g/dL at baseline. An improvement in disease-related anemia is defined as an increase of hemoglobin of 2 g/dLwithout RBC transfusion or erythropoietin support. The primary analysis on this endpoint will be performed among subjects with disease-related anemia at baseline using the Pearson Chi-square test. Disease-related anemia will also be assessed based on the following NCI CTC grade for hemoglobin:

Grade 4: hemoglobin < 6.5 g/dL
Grade 3: hemoglobin >6.5 g/dL but < 8 g/dL
Grade 2: hemoglobin >8.0 g/dL but < 10 g/dL
Grade 1: hemoglobin >10.0 g/dL but < lower limit of the normal
Grade 0: hemoglobin > lower limit of the normal

Numbers (%) of subjects with a maximum grade of 0, 1, 2, 3, or 4 during the study will be summarized and compared between the two treatment groups using the CMH modified ridit score test stratified by baseline grade (0 or >0).

5. Decreased use of RBC transfusion

The number of RBC transfusions in the two-month period prior to study initiation and every 2 months during the study will be calculated for each subject. The average number of RBC transfusions in each two-month period will be obtained for each subject. The primary analysis on this endpoint will be performed using an analysis of covariance (ANCOVA) model with number of transfusions at baseline as a covariate. The total number of units of RBCs transfused will be analyzed similarly as the number of RBC transfusions.

6. Decreased dose of erythropoietin administered

The dose of erythropoietin administered in the two-month period prior to study initiation and every 2 months during the study will be calculated for each subject. The average dose of erythropoietin administered in each two-month period will be obtained for each subject. The primary analysis on this endpoint will be performed using an analysis of covariance (ANCOVA) model with the administered baseline dose as a covariate.

7. Improvement in fatigue as measured by the Brief Fatigue Inventory (BFI)

A global BFI score will be calculated using the arithmetic mean of the nine BFI items for each treatment group at baseline, Cycle 3 and Cycle 6. Change from baseline will be calculated and descriptive statistics will be presented for each treatment group at each time point.

8. Improvement in fatigue as measured by resolution of the pre-existing condition

All fatigue data collected throughout the study will be consolidated and the status of fatigue will be dichotomized into present or absent at each time point for all subjects. Resolution of fatigue is defined as the absence of fatigue if present at baseline. The post treatment status of fatigue (present or absent) will be tabulated by the baseline status for each treatment group.

9. Resolution of other disease-related symptoms
Other disease-related symptoms consist of early satiety due to hepatosplenomegaly, abdominal discomfort due to hepatosplenomegaly, impaired cosmesis due to lymphadenopathy, and impaired mobility due to lymphadenopathy. Among the subjects with at least one of these four symptoms at baseline, the number and percentage of subjects with resolution will be presented for each treatment group. All clinical benefit endpoints will be assessed using the best response achieved during study.

5.7.4 Multiplicity issues regarding secondary efficacy endpoints
(Statistical Analysis Plan: Protocol GL303 Release Date: 3 Aug 2004, page 11).

For all secondary efficacy endpoints, statistical analyses will be conducted only if the analysis of the primary efficacy endpoint is statistically significant at a two-sided 0.05 level after the adjustment of alpha for the interim analysis.
To guard against spurious inflation of the Type I error rate, secondary efficacy endpoints are classified into two categories and a stepwise analysis is proposed within each category.

Category I includes overall response rate, time to progression, survival time, and duration of response. Category II includes all clinical benefit endpoints.

Within Category I, the analyses of efficacy endpoints will be conducted for the ITT population in a stepwise manner to control a family- wise error rate of 0.05 following the order of:
1. Time to progression
2. Overall response rate
Duration of response will be analyzed descriptively only.
Survival time will be analyzed with a later cut-off date (on or prior to 30 June 2006) when all subjects have had an opportunity for a 3- year follow-up from randomization
Each of the above endpoints will be tested at α=0.05 level. If significance is achieved, the test of the next endpoint will be performed. If not, confirmatory conclusions on subsequent endpoints will not be drawn. Similarly, analysis of clinical benefit endpoints in…

7.0 CHANGES TO ANALYSES PLANNED IN THE PROTOCOL
Statistical Analysis Plan: Protocol GL303 Release Date: 3 Aug 2004, page 14.

Changes made to the analyses described in the protocol are summarized below:
- Additional exploratory analyses will be performed on response rate parameters (CR + n-PR rate and CR + n-PR + PR rate) and time-to-event analyses (TTP and survival) using statistical models adjusting for prognostic factors as specified in Section 5.7.2.
- The BFI score over time will not be analyzed using a mixed effect linear model. Missing BFI scores will not be imputed by the last observation carried forward method.
- Statistical testing on survival time will not be performed until all subjects have been followed for a minimum of 3 years.
- No efficacy analysis will be performed on per-protocol population.
- ECOG performance status will be analyzed using the CMH Chi-Square stratified by baseline status.

- An improvement in disease-related anemia will be defined as an increase of hemoglobin of 2 g/dL without RBC transfusion or erythropoietin support. The primary analysis of this endpoint and 2 other endpoints, resolution of B-symptoms, and resolution or reduction of massive splenomegaly will be performed using the Pearson chi-square test among all subjects with the respective condition at baseline.

The following change is made to the analysis Genta proposed to the Agency on March 4, 2003:

- B-Symptoms are composed of fever and night sweats. Improvement in impaired mobility due to lymphadenopathy, impaired cosmesis, abdominal discomfort due to hepatosplenomegaly, and early satiety are separated into another clinical benefit endpoint and will be analyzed by descriptive statistics only.

Summary of efficacy findings for protocol GL303

GL303 N= 241 Results	**G3139 plus Flu/Cy (120) n (%)**	**Flu/Cy (121) n (%)**	**P value**
CR	11	3	0.03 [a]
nPR	9	5	
CR + nPR	20 (16.7)	8 (6.6)	0.025 [b] 0.016 [a]
PR	29	46	
Overall Response: CR + nPR + PR	49 (41)	54 (45)	NSD
Time to progression- median (months)	6.1	9.0	NSD
Overall survival – median (months)	34	33	NSD
Duration of response (ORR)	14.6	15.2	NSD
Any "clinical benefit" (symptom resolution defined by Genta)			NSD
Symptom-free interval (CR+nPR+PR) median - days	400	502	NSD
Symptom-free interval (CR+nPR+PR) mean - days	464 (1SD 284)	464 (1SD 265)	NSD
Symptom-free interval (CR+nPR) median - days	755	641	
Symptom-free interval (CR+nPR) mean - days	648	635	
Symptom-free interval (PR) median - days	315	437	
Symptom-free interval (PR) mean - days	337 (1SD 236)	435 (1SD 254)	

NSD = no significant difference; 1SD = one standard deviation

Genta analysis of response (CR+nPR) by age

Age group	G3139 plus Flu/Cy		Flu/Cy	
	N	n (CR+nPR)	N	n (CR+nPR)
< 65 years	67	12 (18%)	69	2 (3%)
≥ 65 years	53	8 (15%)	52	6 (11.5%)

Table 14.2.4.1.1, CSR GL303

Genta analysis of response (CR plus nPR) by gender

Gender	G3139 plus Flu/Cy N = 120		Flu/Cy N = 121		Odds ratio
	N	n (%)	N	n (%)	
Male	89	18 (20.2)	89	6 (6.7)	3.5
Female	31	2 (6.5)	32	2 (6.3)	1.03

Table 14.2.4.2.1, ISE

Genta analysis of response (CR plus nPR) by baseline hemoglobin

Baseline hemoglobin	G3139 plus Flu/Cy N = 120		Flu/Cy N = 121	
	N	n (%)	N	n (%)
< 11 g/dL	32	2 (6.3)	39	1 (2.6)
≥ 11 g/dL	87	18 (20.7)	82	7 (8.5)

Table 14.2.4.8.2, ISE

Genta analysis of response (CR plus nPR) by baseline platelet count

Baseline platelet count	G3139 plus Flu/Cy N = 120		Flu/Cy N = 121	
	N	n (%)	N	n (%)
< 100,000/uL	43	2 (4.7)	43	0
≥ 100,000/uL	77	18 (23.4)	78	8 (10.3)

Table 14.2.4.9.1, ISE

Genta analysis of response (CR plus nPR) by baseline fludarabine sensitivity

Baseline Flu sensitive	G3139 plus Flu/Cy N = 120		Flu/Cy N = 121	
	N	n (%)	N	n (%)

YES	51 13 (25.5)	50 3 (6.0)
NO	69 7 (10.1)	71 5 (7.0)

Table 14.2.4.11.1, ISE

Genta analysis of response (CR plus nPR) by baseline LDH level

Baseline LDH level	G3139 plus Flu/Cy N = 120		Flu/Cy N = 121	
	N	n (%)	N	n (%)
Non-elevated	63	16 (25.4)	63	5 (7.9)
Elevated	53	4 (7.5)	52	3 (5.8)

Table 14.2.4.12.1, ISE

References

[1] Cheson BD, Bennett JM, Rai KR, Grever MR, Kay NE, Schiffer CA, Oken MM, Keating MJ, Boldt DH, Kempin SJ, Foon KA: Guidelines for clinical protocols for chronic lymphocytic leukemia: Report of the NCI-sponsored Working Group. Amer J Hematol 1988; 29: 152.

[2] National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, Rai K. Blood 1996; 87: 4990-4997.

[3] Robertson LE, Huh YO, Butler JJ, Kantarjian H, Keating MJ. Response assessment in chronic lymphocytic leukemia after fludarabine plus prednisone: clinical, pathologic, immunophenotypic, and molecular analysis. Blood 1992;80:29-36.

[4] Keating MJ, O'Brien S, Lerner S, Koller C, Beran M, Robertson LE, Freireich EJ, Estey E, and Kantarjian H. Long-Term Follow-Up of Patients With Chronic Lymphocytic Leukemia (CLL) Receiving Fludarabine Regimens as Initial Therapy Blood 1998; 92: 1165-1171.

[5] Keating MJ. American Society of Hematology Education Book 2003, page 166.

[6] O'Brien SM, Kantarjian HM, Cortes J, Beran M, Koller CA, Giles FJ et al. Results of the Fludarabine and Cyclophosphamide Combination Regimen in Chronic Lymphocytic Leukemia. J Clin Oncol 2001; 19:1414-1420.