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GENASENSE®

(oblimersen sodium) Injection

Advisory Committee Briefing Document

NDA 21-874

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or specialized term	Explanation
APTT	activated partial thromboplastin time
AUC	area-under-the-concentration curve
Bax	proapoptotic protein
bcl-2	messenger ribonucleic acid (mRNA) name for *BCL2*
BCL2	B-cell leukemia/lymphoma 2 gene
Bcl-2	B-cell lymphoma break point 2; a protein that suppresses apoptosis and is upregulated in many types of tumors
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CL	clearance
CR	complete response
C_{ss}	concentration at steady state
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DNA	deoxyribonucleic acid
DTIC	dacarbazine
ECOG	Eastern Cooperative Oncology Group
eg	for example
ELISA	enzyme-linked immunosorbent assay
FCM	fludarabine, cyclophosphamide, and mitoxantrone
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FLAG	fludarabine, cytarabine, and G-CSF
FC	fludarabine and cyclophosphamide
GFC	Genasense plus fludarabine and cyclophosphamide
ie	that is
ITT	intent-to-treat
K_i	disassociation constant for the enzyme-inhibitor complex
LDH	lactate dehydrogenase
mRNA	messenger ribonucleic acid
N-1	the 17-mer metabolite of oblimersen
N-2	the 16-mer metabolite of oblimersen
NCI-CTC	National Cancer Institute Common Toxicity Criteria

Abbreviation or specialized term	Explanation
NCI-WG	National Cancer Institute Working Group
NDA	New Drug Application
nPR	nodular partial response
ODAC	Oncology Drug Advisory Committee
PDUFA	Prescription Drug User Fee Act
PR	partial response
RBC	red blood cell(s)
RNA	ribonucleic acid
Rnase H	ribonucleic acid nuclease H
RT-PCR	reverse-transcription polymerase chain reaction
SD	standard deviation
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life
vs.	versus
V_z	volume of distribution
WBC	white blood cell(s)

EXECUTIVE SUMMARY

OVERVIEW

ODAC has been asked for advice regarding the Sponsor's request for accelerated approval of Genasense® (oblimersen sodium) plus fludarabine and cyclophosphamide (GFC) for patients with relapsed or refractory chronic lymphocytic leukemia (CLL).

The Genasense application is the first NDA in CLL to include a randomized, controlled trial. The NDA also contains data from a Phase 1-2 trial of Genasense alone in 40 patients that was conducted to evaluate single-agent safety and activity (Study GL208). Additional safety data from approximately 1,000 patients treated with Genasense in other oncology trials were also submitted. Lastly, after discussion with the FDA, the Sponsor has initiated a confirmatory randomized trial.

The pivotal trial in 241 patients (Study GL303) met its primary endpoint: the addition of Genasense to standard chemotherapy (ie, fludarabine and cyclophosphamide [FC]) significantly increased the proportion of patients who achieved a complete response (CR) or nodular partial response (nPR) (17% in the Genasense plus FC group versus [vs.] 7% in the FC group; $p = 0.025$). The clinical responses and bone marrow histopathology were centrally reviewed and, in contrast to prior studies in CLL, computed tomography (CT) re-imaging was required to confirm CR/nPR in patients who had baseline abnormalities. All CR/nPRs in both treatment groups were durable (ie, lasting 6 months or longer from time of initial response). Remission duration was significantly longer in CR/nPR patients who received Genasense compared with patients who received chemotherapy alone (median not yet reached vs. 22 months, respectively; $p = 0.03$). All but one CR/nPR were associated with durable relief of disease-related symptoms. Overall response rate, time to disease progression, and survival were not significantly different between treatment groups.

Genasense was superior across all prospectively defined strata. Exploratory analysis suggested that patients who remained sensitive to chemotherapy may have derived the greatest benefit. The Sponsor will confirm this benefit in a randomized study in patients with CLL who have not previously received chemotherapy (Study GL305). The protocol for this trial was submitted to the FDA for a Special Protocol Assessment in December 2005, and the trial was initiated in July 2006.

The FC standard of care is highly immunosuppressive and myelosuppressive. The addition of Genasense to FC did not increase the incidence of neutropenia or anemia. Genasense-treated patients experienced an increased incidence of thrombocytopenia, which occurred primarily in the first cycle, and an increased incidence of catheter-related events. A fatal event due to an infusion-related

reaction and tumor lysis syndrome occurred in 1 patient each in the Genasense arm (both in Cycle 1).

The safety profile of Genasense in CLL is supported by data from more than 1,000 patients with hematologic or solid tumors treated in 18 completed clinical trials. Adverse events are manageable and familiar to clinicians in the oncology setting who observe similar events with standard-of-care chemotherapy.

The addition of Genasense to FC significantly increases the proportion of patients with relapsed or refractory CLL who can achieve CR/nPR. This level of response is associated with a significantly superior degree of durable and complete symptomatic relief.

GENASENSE AND Bcl-2 IN CLL

Genasense downregulates Bcl-2, a protein that is believed to block apoptosis. By downregulating one of the central regulators of apoptosis, Genasense acts to enhance the effectiveness of cancer chemotherapy. This observation is supported by a large number of preclinical studies.

Numerous studies have demonstrated that CLL is characterized by high expression of Bcl-2 in almost all patients.(1,2,3,4,5,6,7,8) Moreover, Bcl-2 has recently been shown to play a central role in the pathogenesis of CLL. In CLL, Bcl-2 downregulation may directly lead to lymphoid cell death,(9,10) and Genasense as a single agent has been associated with tumor lysis syndrome in this disease.

RELAPSED/REFRACTORY CLL IS AN UNMET MEDICAL NEED

In its earliest stages, CLL may remain indolent for prolonged periods. However, in the relapsed setting, CLL tends to be relentlessly progressive and refractory to chemotherapy, and it chiefly afflicts an older patient population with multiple comorbid conditions. Relapsed patients with late-stage disease tend to be symptomatic: fever, fatigue, night sweats, pain, impaired cosmesis from lymphadenopathy, and complications related to hepatosplenomegaly are common. The most frequent cause of death in these patients is recurrent infection due to pancytopenia.

In June 2003, FDA granted Fast Track designation to the Gensense plus FC combination, noting that CLL "…is a serious life-threatening disease complicated by an increased risk of infection, serious anemias, and thrombocytopenia for which there is no cure for the majority of patients." The designation further noted that the Genasense development program that included the pivotal trial in this NDA "…has the potential to address an unmet medical need."

CR/nPR IS A STRINGENT ENDPOINT IN CLL

No single drug or drug combination has ever yielded a survival improvement in CLL at any stage of the disease. From a regulatory standpoint, time to progression

has never been the basis of initial approval for any drug in any form of leukemia — acute or chronic. In CLL, no drug has ever shown an intent-to-treat symptomatic benefit.

In contrast, response rate — particularly the rate of durable complete responses — has commonly been the basis for the initial approval of leukemia drugs in the United States. (In chronic myelogenous leukemia, hematologic and/or cytogenetic responses have been acceptable endpoints.) In this regard, CLL has been evaluated somewhat differently, since overall response (generally comprised of PRs) has qualified as a primary endpoint for accelerated approval. Most recently, alemtuzumab (Campath®) received accelerated approval in 2001 with a 2% CR rate and a 31% PR rate in a fludarabine-refractory population. Alemtuzumab is increasingly being used in a setting of minimal residual disease, because it appears to be much less effective in patients with bulky lymphadenopathy.(11,12,13)

In acute leukemia, CR is typically a full approval endpoint that does not require further documentation of clinical benefit. In CLL, nodular CR (also referred to as nodular PR) has been well characterized. An nPR is a CR by virtually all criteria, including complete disappearance of all signs of disease (including recovery of blood counts) and resolution of constitutional symptoms. The single difference is that focal aggregates (nodules) of lymphoid cells are apparent in the confirmatory bone marrow biopsy for an nPR. Historical data show that the outcome in patients with CLL who achieve nPR is similar to that in patients who achieve CR.(14,15) More importantly, the outcome is far superior to that of patients whose best response is a PR, as shown in Figure 1.

Figure 1: Survival after treatment with fludarabine-containing regimens in sequential studies by best response in previously untreated patients

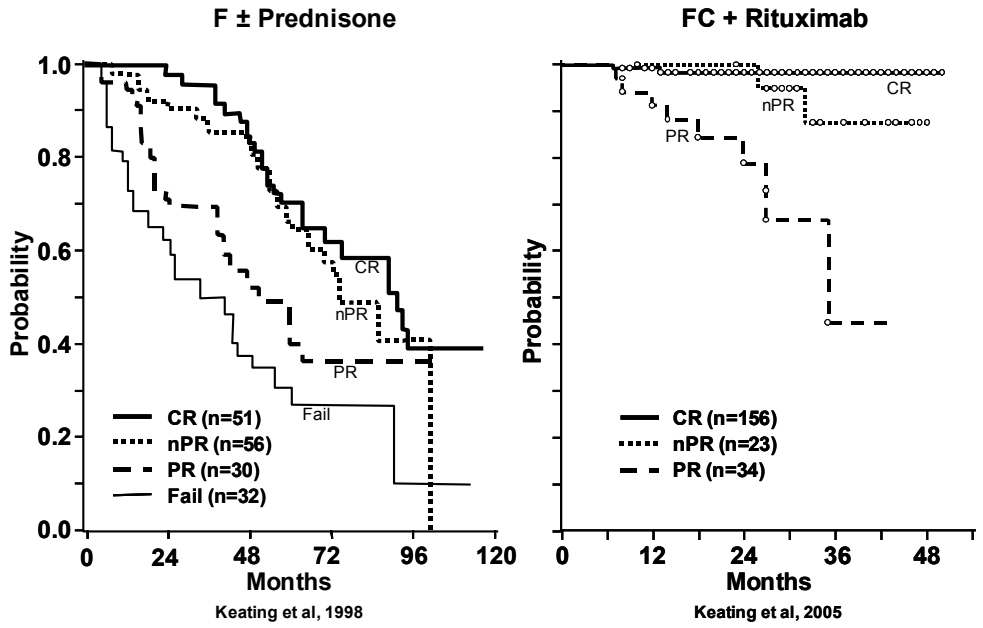


Figure 1 shows data from 2 large, sequentially conducted studies at M.D. Anderson Cancer Center that confirm the favorable outcome for previously untreated patients who achieved CR or nPR after treatment with fludarabine-containing regimens.(14,15) Patients with an nPR attain all the clinical benefit that accrues to patients with CR. In contrast, patients whose best response is PR — a population that has comprised the majority of patients in regulatory-approval studies — fared markedly worse. These findings are reconfirmed in the pivotal trial of Genasense in this NDA.

In the Genasense pivotal trial, clinical response, disease progression, and bone marrow histopathology were determined by blinded central review. Although CT/ultrasound imaging was not required by NCI-WG criteria,(16) re-imaging was required by protocol in the Genasense trial to confirm CR/nPR in patients with abnormalities identified at baseline by CT/ultrasound; 74% and 75% of patients in the GFC and FC groups, respectively, had abnormal radiographic findings at baseline.

CLL REGULATORY HISTORY

Two drugs have been approved for the treatment of patients with relapsed/refractory CLL: fludarabine (Fludara®) in 1991 and alemtuzumab (Campath®) in 2001. Both agents were approved on the basis of nonrandomized trials that included fewer than 100 patients in total and employed overall response (primarily PR) as the primary endpoint. Both drugs were associated with substantial toxicity.

In its deliberation on alemtuzumab in 2000, which immediately preceded the design of the Genasense pivotal trial, ODAC voted unanimously in favor of Question 1, namely that "…response rate [almost exclusively PRs], duration of response, and clinical outcome [as demonstrated in a post hoc, responders-only analysis] were reasonably likely to predict clinical benefit." In more recent deliberations (eg, the FDA Workshop on Clinical Trial Endpoints in Acute Leukemia, 24 Jun 2005), the FDA has viewed "durable CR" as the preferred primary endpoint for these patients.

Based on ODAC's position, the Sponsor proposed that a significant increase in CRs/nPRs that are durable, associated with durable clinical benefit, and significantly superior in duration to an accepted standard of care in a prospective randomized trial is likely to be predictive of clinical benefit and should serve as the basis for accelerated approval of Genasense. The Sponsor has initiated a study in previously untreated patients as agreed with the FDA by Special Protocol Assessment (GL305).

GENASENSE REGULATORY HISTORY

In Dec 2003, the Sponsor submitted an NDA for Genasense plus dacarbazine in patients with advanced, metastatic melanoma. The application was reviewed by ODAC in May 2004 and failed to secure a majority vote to recommend approval.

The analysis included in the NDA was conducted with only 7 months of minimum patient follow-up. In 2005, the Sponsor completed 24 months of minimum follow-up, and the principal efficacy results of the final analysis are shown Table 1. The study approached but did not quite achieve statistical significance for its primary endpoint (overall survival, ITT analysis).(17) All secondary endpoints were achieved, including (for the first time in melanoma) significant increases in CR and durable responses. Superiority in a number of these endpoints is also evident in the Genasense CLL NDA. Importantly, for more than 500 patients with normal LDH at baseline (LDH is an accepted prognostic variable in melanoma), the survival benefit at 2 years was highly significant (p = 0.018).(17)

Table 1: Summary of efficacy findings in pivotal Genasense melanoma study with minimum 24-month follow-up

Endpoint	Genasense/ dacarbazine	Dacarbazine	p
Complete response, n (%)	11 (2.8)	3 (0.8)	0.03
Durable response, n (%)	28 (7.3)	14 (3.6)	0.03
Overall response (CR + PR), n (%)	52 (13.5)	29 (7.5)	0.007
Progression-free survival, months	2.6	1.6	0.0007
Overall survival, months			
ITT[a]	9.0	7.8	0.077
Serum LDH ≤ 1.1 x ULN[b]	11.4	9.7	0.018

[a] N = 386 in the Genasense/dacarbazine group and N = 385 in the dacarbazine group
[b] N = 261 in the Genasense/dacarbazine group and N = 247 in the dacarbazine group

CLINICAL EFFICACY OF GENASENSE IN RELAPSED/REFRACTORY CLL

The clinical efficacy of Genasense in patients with relapsed/refractory CLL is based on 2 trials:

- a Phase 1-2, multicenter, open-label study (GL208) of Genasense administered alone, which determined the safety, maximum tolerated dose, and single-agent activity
- a Phase 3, randomized, multicenter, open-label efficacy/safety study (GL303) of Genasense in combination with FC vs. FC alone

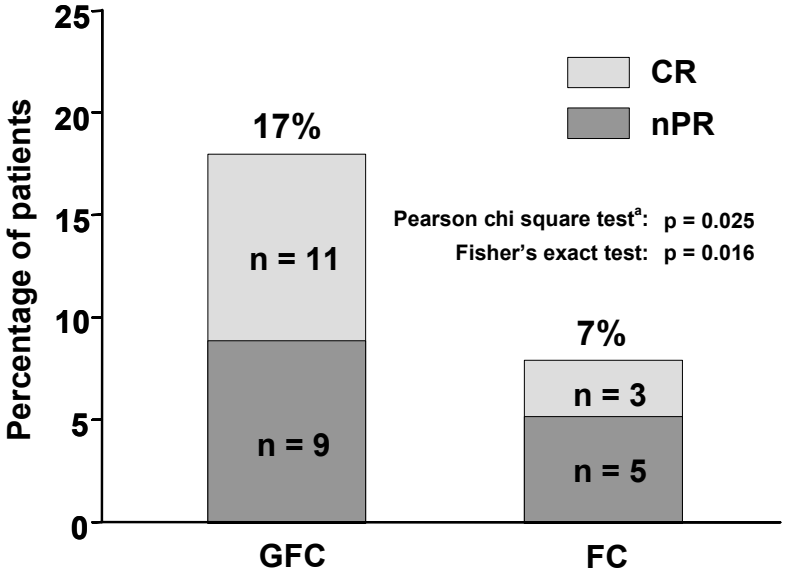
In the noncomparative Phase 1-2 trial, a total of 40 patients were enrolled and treated. Approximately 50% of evaluable patients displayed evidence of anti-leukemic activity, including such findings as a reduction in hepatosplenomegaly and lymphadenopathy and lowering of elevated lymphocyte counts. The occurrence of tumor lysis syndrome in 2 patients also supports the single-agent

activity of Genasense in this population. Of 26 patients evaluable for response as defined in the analysis plan, 2 (8%) patients achieved a partial response. Notably, both patients had previously been treated with ≥ 4 chemotherapy regimens.

In the randomized Phase 3 trial, 241 patients were randomized and 230 patients were treated with either Genasense (3 mg/kg/d on Days 1 – 7) in combination with fludarabine (25 mg/m^2/d on Days 5 –7) and cyclophosphamide (250 mg/m^2/d on Days 5 – 7) or the fludarabine/cyclophosphamide (FC) regimen alone. The primary efficacy endpoint was the proportion of patients who achieved CR or nPR as determined by an external clinical expert blinded to the study treatment when each patient had been followed for at least 6 months after ending protocol therapy. Secondary efficacy endpoints included overall response rate, duration of response, time to progression, clinical benefit, and survival.

The Phase 3 trial achieved its primary endpoint. The addition of Genasense to FC resulted in a 2.4-fold increase in the proportion of patients who achieved a CR or nPR (p = 0.025; see Figure 2).

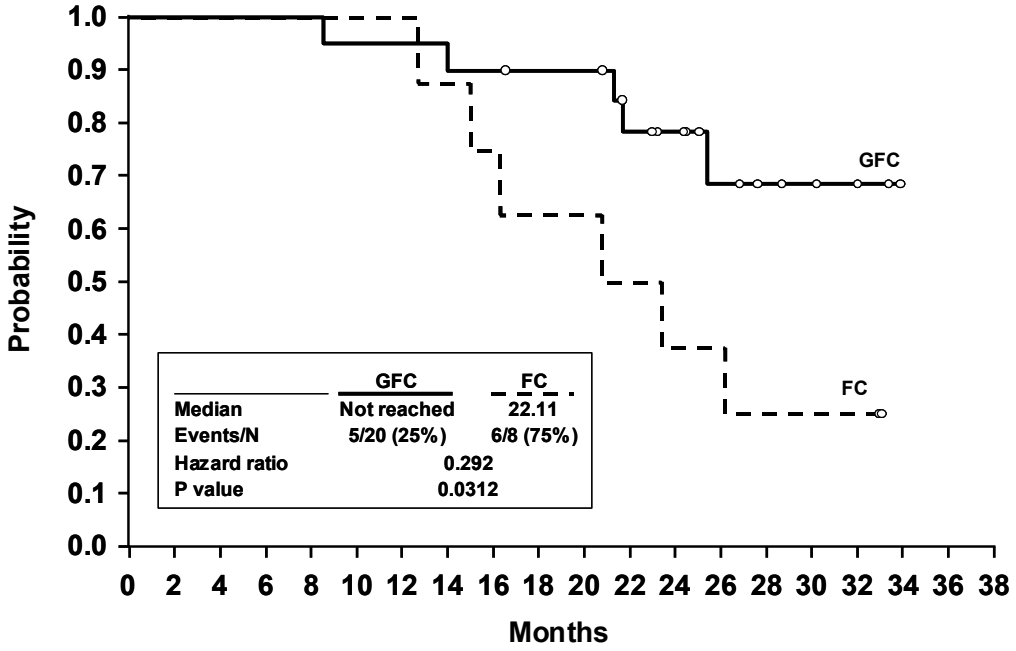
Figure 2: Primary endpoint (CR/nPR rate) in the Genasense pivotal trial: ITT Population



[a] Two-sided continuity-corrected

All CRs/nPRs in both treatment groups were shown to be "durable" (ie, lasting 6 months or longer). The duration of CR/nPR was significantly longer in patients treated with the Genasense plus FC regimen than the FC regimen (median not reached vs. 22 months, respectively; p = 0.03; see Figure 3).

Figure 3: Duration of CR/nPR in the Genasense pivotal trial



The Genasense plus FC regimen yielded numerically superior results for CR/nPR in all prespecified stratification groups. Exploratory analysis suggested that certain groups disproportionately benefited from the addition of Genasense to FC, particularly those who remained chemosensitive, ie, were fludarabine sensitive, had been treated with not more than 2 prior regimens, or had a duration of response to last prior therapy > 6 months in duration (see Table 2). This finding was not observed in the FC group.

Table 2: CR/nPR by prospectively specified stratification groups in the Genasense pivotal trial

	GFC n (%)	FC n (%)
Prior fludarabine		
Relapsed (sensitive)	13 (25)	3 (6)
Refractory	7 (10)	5 (7)
Number of prior regimens		
1-2	14 (23)	4 (6)
≥ 3	6 (10)	4 (7)
Response to last therapy		
> 6 months	12 (22)	3 (6)
≤ 6 months	8 (12)	5 (7)

With a single exception, all CRs/nPRs in both treatment groups were associated with durable relief (ie, a minimum of 6 cumulative symptom-free months) of disease-related symptoms, including fever, night sweats, fatigue, abdominal discomfort or early satiety due to hepatosplenomegaly, impaired cosmesis due to lymphadenopathy, impaired mobility due to lymphadenopathy, and "other."

In the Genasense pivotal trial, the proportion of patients who achieved durable symptomatic relief was significantly superior for patients who attained CR/nPR compared with patients whose best response was PR ($p < 0.01$; see Table 3). Moreover, this trial also showed that very few patients whose best response was less than a PR achieved any level of durable symptomatic relief; durable clinical benefit in these patients was not observed.

Table 3: Association between level of response and durable relief of disease-related symptoms irrespective of treatment in the Genasense pivotal trial

No. of patients	CR/nPR n (%)	PR n (%)	< PR n (%)
Symptomatic at baseline	18	61	121
Symptom-free for ≥ 6 months	17 (94)[a]	36 (59)	7 (6)

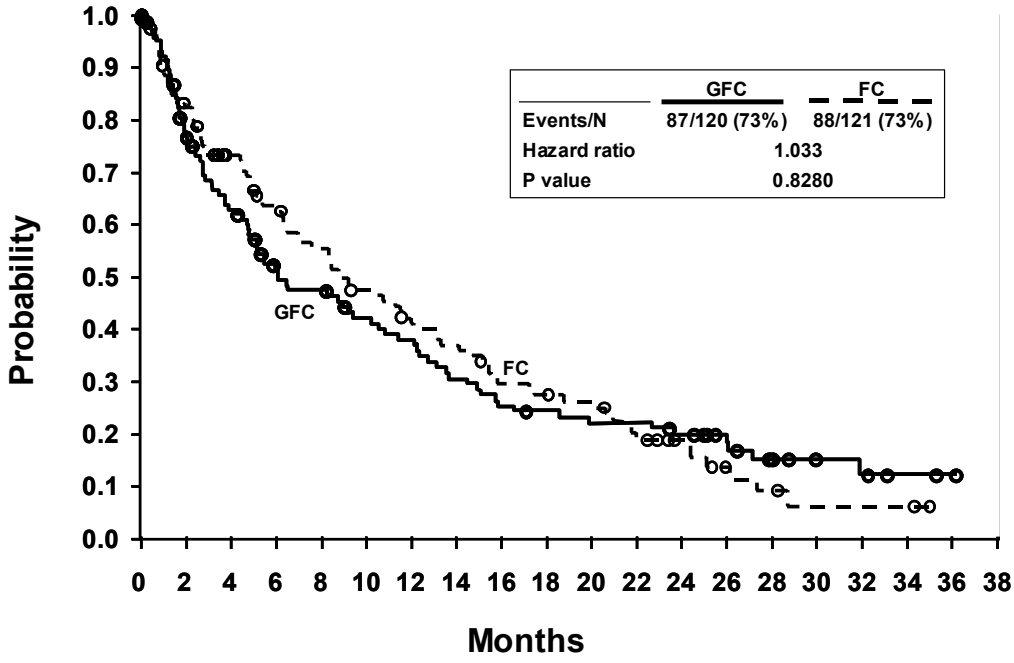
$p < 0.0001$ for CR/nPR vs. PR vs. < PR

$p < 0.01$ for CR/nPR vs. PR

[a] Excludes 1 patient in the GFC group for whom fatigue was reported after 5 months without symptoms

There was no significant difference in overall response rate (CR + nPR + PR) in patients treated with FC with and without Genasense (41% vs. 45%, respectively). There was also no significant difference in time to progression (see Figure 4).

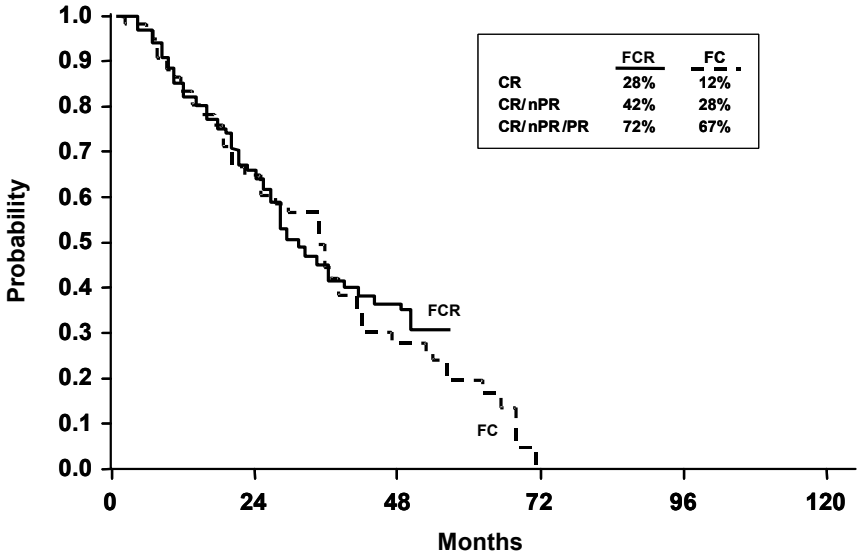
Figure 4: Time to progression in the Genasense pivotal trial: ITT Population



Two factors may be relevant for consideration of time to progression in the relapsed/refractory setting of CLL.

- **A significant increase in CR/nPR is not sufficient to shift the median time to progression:** Disease progression is rapid in patients with a PR or less. In the Genasense pivotal study, the percentage of patients with a PR or less totalled 88% across the 2 treatment groups, and the median time to progression was not affected by patients with CR/nPR.
- **Time to progression may not be a sensitive endpoint in relapsed or refractory CLL:** Doubling of the CR rate in 2 large, nonrandomized, sequential, single-center trials showed that the addition of rituximab to FC yielded a proportional increase in CR rate and CR/nPR rate with no difference in overall response rate — similar to findings in the Genasense pivotal study — but did not change time to progression (see Figure 5).(15,18,19)

Figure 5: Time to progression: Significant increase in CR and CR/nPR rate without significant improvement in time to progression or overall response rate with addition of rituximab to FC (Adapted from Wierda et al, 2006)



Overall, the primary endpoint — a statistically significant increase in the proportion of patients who achieved a CR/nPR as determined based on blinded external review — was met in the Genasense pivotal trial and that endpoint was associated with durable symptomatic relief. No other randomized trials reported in the setting of relapsed or refractory CLL have shown superiority with any other regimen.

CLINICAL SAFETY

The safety profile of Genasense administered alone in patients with CLL is clearly described in the Phase 1-2 study in which Genasense was administered as monotherapy as a 5- to 7-day continuous intravenous infusion to 40 patients with relapsed or refractory CLL. In particular, 14 patients were treated in Phase 1 with Genasense 3 to 7 mg/kg/d to determine the maximum tolerated dose, and 26 patients were treated in Phase 2 with the maximum tolerated dose of 3 mg/kg/d.

Most patients experienced adverse events, the most common being fever (13 [32.5%] patients); fatigue (12 [30%] patients); cough and hypotension (8 [20%] patients each); and anemia, thrombocytopenia, nausea, and night sweats (7 [17.5%] patients each). Most adverse events were Grade 1 or Grade 2 (NCI-CTC, Version 2.0).

In the Genasense pivotal trial, the side effect profile of Genasense (3 mg/kg/d by 7-day continuous intravenous infusion) in combination with FC in the 115 treated patients was compared with that observed in the 115 patients treated with FC alone. Nausea, thrombocytopenia, fever, fatigue, anemia, and vomiting (presented in decreasing incidence) occurred in at least 30% of patients in the Genasense

plus FC group. All of these events except fever and vomiting similarly occurred in at least 30% of patients in the FC group. Among the hematologic events shown, only thrombocytopenia occurred at a greater incidence in the Genasense plus FC group than in the FC group (49% vs. 40%, respectively). Among the nonhematologic events shown, nausea, pyrexia, fatigue, and vomiting occurred in at least 10% more patients in the Genasense plus FC group than in the FC group, with the most notable difference between treatment groups observed for nausea (GFC group, 72%; FC group, 48%). As observed in the Phase 1-2 study, most adverse events were Grade 1 or Grade 2.

Although 2 randomized studies have now convincingly shown that the FC combination is significantly superior to fludarabine alone for CR induction in previously untreated patients with CLL (see Figure 6),(20,21) FC is a relatively toxic standard of care for both previously untreated and relapsed/refractory CLL. Fludarabine is associated with severe bone marrow suppression (namely, anemia, thrombocytopenia, and neutropenia), life-threatening and occasionally fatal autoimmune hemolytic anemia, tumor lysis syndrome, and infection (including serious opportunistic infections). With cyclophosphamide, second malignancies, immunosuppression, neutropenia, hemorrhagic disorders (colitis, cystitis, and ureteritis), and acute cardiac toxicity are of particular concern.

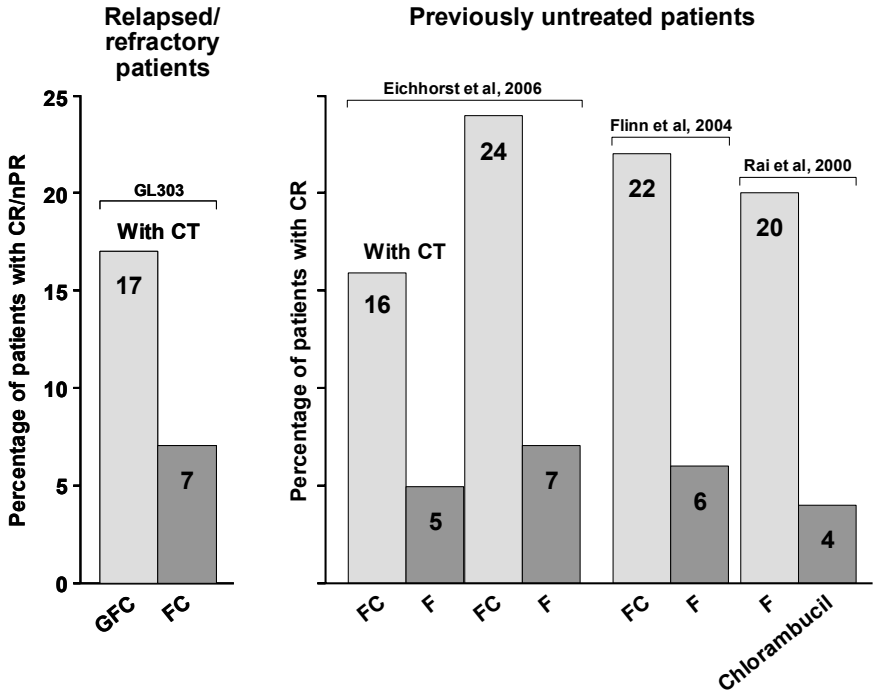
BENEFIT/RISK EVALUATION

The Genasense development program in CLL prospectively tested the hypothesis that targeting Bcl-2 should increase leukemia-cell death induced by standard-of-care chemotherapy.

The achievement of CR is conventionally accepted as evidence of clinical benefit for patients with leukemia. In the large, randomized pivotal study, the addition of Genasense to standard FC therapy increased the CR/nPR rate from 7% to 17% — a prospectively specified and statistically significant difference. The response to FC was lower than estimated based on earlier reports from nonrandomized trials. The difference is readily explained by differences in patient populations, as well as the rigor of the assessments in this study. For example, historical experience at the time this trial was designed suggested that the CR/nPR rate with FC could be as high as 28% (see Figure 5).(19) In the original study of the FC combination in this setting, approximately 30% of patients previously treated with fludarabine were refractory to fludarabine, as compared to approximately 60% of patients in the Genasense pivotal study. Other key differences include a single-center vs. multiple-center design, referral patterns, and more stringent response criteria (eg, blinded central review and CT imaging). The addition of CT/ultrasound imaging alone has been shown to reduce the CR rate to FC by approximately 30% in a recently reported randomized trial in previously untreated patients with CLL (see Figure 6).(20) Notwithstanding these issues, the observed level of response in the Genasense pivotal trial falls well within comparable proportions achieved with other effective therapies (including FC) evaluated in previously untreated patients in randomized controlled trials (see Figure 6).(20,21,22) Both the absolute and

relative magnitude of the increase (~2.5-fold) in the Genasense pivotal trial are in accord with findings in other randomized trials.

Figure 6: Response in the Genasense pivotal trial compared with response in recent, large, randomized trials in previously untreated patients



Exploratory analyses of prospectively specified stratification factors in the Genasense pivotal trial suggested that the benefit/risk ratio could be further improved by administration to patients who remained sensitive to chemotherapy. (Notably, the response to FC was low irrespective of the amount of or response to prior therapy.) These patients appeared to disproportionately benefit, with nonrefractory patients achieving nearly a 4-fold increase in the CR/nPR rate. This benefit will be comprehensively evaluated in the ongoing confirmatory study of Genasense in previously untreated patients (GL305).

As in acute leukemia, the benefit to patients with relapsed/refractory CLL accrued to patients who responded. The major risk of the combination treatment regimen lies with the associated FC chemotherapy, which is both myelosuppressive and immunosuppressive in compromised patient populations.

A unique advantage for an anti-leukemic agent is the absence of an increase in neutropenia despite a significant increase in CRs, especially for a drug that will be used in older patients with existing cytopenias and multiple comorbid conditions. This is a key benefit with the addition of Genasense to FC chemotherapy. The addition of Genasense to FC also does not exacerbate anemia, a common problem in patients with CLL. The addition of Genasense to FC increased the incidence of thrombocytopenia and platelet transfusions. However, Grade 3 and Grade 4

bleeding events (3.5% and 2% in the GFC and FC groups, respectively) were not similarly increased.

Finally, it is important to note that while symptomatic relief can be achieved in some patients who achieve PR, patients who achieve CR/nPR not only attain durable symptomatic relief, they also have no evidence of leukemia. Thus, they have complete disappearance (rather than a 50% decrease with a PR) in lymphadenopathy and hepatosplenomegaly, as well as recovery of blood counts — benefits that do not accrue to patients whose best response is PR. Similar to the experience with rituximab (see Figure 5),(19) this trial did not demonstrate an improvement in time to progression or overall response rate in relapsed or refractory patients despite an increase in CR/nPR of similar relative magnitude.

Adverse experiences in the Genasense pivotal trial were qualitatively similar to reactions observed with chemotherapy used in patients with relapsed/refractory CLL. Infusion-related reactions and tumor lysis syndrome that proved dose-limiting in Phase 1 were rare in the pivotal trial. Tumor lysis is a consequence of any effective anti-leukemic therapy and does not represent a unique risk. Physicians who treat CLL are already familiar with qualitatively similar infusion-related reactions that are associated with other marketed or investigational agents, including rituximab, alemtuzumab, and flavopiridol. As such, measures that can prevent or ameliorate the severity of such events are generally understood.

In addition to the patients treated in the CLL program, the adverse experience profile for Genasense has been characterized in more than 1000 patients with other diseases. This experience indicates that side effects related to the drug are predictable and manageable, and that the agent can be safely combined with cytotoxic chemotherapy.

In summary, the Sponsor proposes that a significant increase in CRs/nPRs that are durable, associated with durable clinical benefit, and significantly superior in duration to an accepted standard of care in a prospective randomized trial is likely to be predictive of clinical benefit and should serve as the basis for accelerated approval of Genasense. The Sponsor will confirm this benefit in an ongoing randomized trial.

Genasense in combination with FC offers a favorable benefit/risk profile that makes this combination a valuable treatment option for patients with relapsed or refractory CLL who have previously received fludarabine.

GENASENSE IN CLL

1. INTRODUCTION

1.1 Rationale for the Development of Genasense

In the 1990s, the increasing importance of apoptosis — a series of biochemical reactions that lead to cell death — in cancer growth and progression was extensively documented in the literature. This research suggested that cancer was characterized by an imbalance between the proportion of cells that lived or died.(23) Moreover, even slight imbalances in the relative fraction of cancer cells that survived were sufficient to cause overgrowth of the tumor and death of the patient. Since then, considerable efforts have been directed towards identifying proteins that are critical regulators of cell survival.

Bcl-2 protein is now recognized as a central regulator of apoptosis.(24) Originally described in association with a chromosomal translation observed in B-cell lymphoma, the BCL2 gene was found to inhibit cell death.

Bcl-2 is normally found within mutiple intracellular compartments, especially the inner mitochondrial membrane. Although multiple effects have been described, current data suggest that Bcl-2 negatively regulates either the size or voltage potential of a mitochondrial transmembrane pore by interacting with the pro-apoptotic protein Bax.(25,26)

The Bcl-2/Bax-regulated pores are functionally similar to a binary switch; that is, the switch is either “open” or “closed” (similar to an axon potential). In the “open” configuration, cytochrome C and calcium are released into the cytoplasm, which initiates caspase activation and irreversibly commits the cell to apoptotic death.(27,28,29,30)

By controlling the pores through which cytochrome C is released, Bcl-2 negatively regulates apoptosis. As such, increased expression of Bcl-2 essentially acts as a survival factor for cancer cells. Thus, Bcl-2 is a fundamental (although not sole) cause of both inherent and acquired resistance of cancer cells to chemotherapy.(31)

Bcl-2 Expression in CLL

CLL was chosen as a target for an anti-Bcl-2 therapy for 3 reasons:

1. Bcl-2 is ubiquitously expressed in leukemic cells obtained from almost all patients with CLL.(1,2,3,4,5,6,7,8) Moreover, levels of Bcl-2 expression in CLL cells are typically higher relative to any other B-cell neoplasm.(3)
2. Epidemiologic data have suggested that relatively higher levels of Bcl-2 expression in CLL cells are associated with less favorable outcome.(4)

3. Bcl-2 is directly related to the pathogenesis of CLL. This finding is supported by recent data from the laboratory of Carlo Croce that shows genetic abnormalities in human CLL cells that results in the loss of specific micro RNAs (miR-15 and miR-16).(9,10) The target of these regulatory molecules was recently shown to be Bcl-2. Conversely, re-introduction of these Bcl-2 regulators induced apoptosis in a murine lymphoid leukemia.(9) Lastly, the laboratory of Scott Lowe has shown that transfection of Bcl-2 into murine lymphoma cells confers a multidrug- resistant phenotype, changing a lymphoma that was previously curative with either alkylating agents or taxanes to a uniformly lethal illness.(32)

Antisense as a Pharmacologic Strategy

Antisense drugs are comprised of short sequences (ie, usually 14 to 24 nucleotides) of DNA that have been chemically modified to improve certain pharmaceutical properties. For example, unmodified DNA typically has a plasma half-life ($t_{1/2}$) of several minutes after injection. Genasense is a phosphorothioate compound that simply substitutes a sulfur atom for a nonbridging oxygen atom in the ribose sugar backbone of DNA, which markedly increases the half-life.

Antisense drugs are designed to limit or halt production of a specific protein. The bases of an antisense drug are comprised of nucleotides that are engineered in a sequence that is complementary to the normal ("sense") strand of messenger ribonucleic acid (mRNA), which is the intermediate precursor to final translation of the protein. When an antisense drug binds to its complementary sequence of mRNA, the mRNA is enzymatically cleaved, which prevents translation of the protein.

Genasense targets the *bcl-2* mRNA. The goal of Genasense therapy is to relieve the block in apoptosis associated with Bcl-2 expression and thus maximize the effectiveness of co-administered anticancer therapy.

1.2 Relapsed or Refractory CLL

CLL is the most common form of leukemia in adults in Western countries. It is estimated that more than 10,000 new cases will be reported in 2006 in the United States alone.(33) CLL occurs primarily in middle-aged and elderly adults, with increasing frequency in successive decades of life. In the 2000- to 2003-period, the median age at time of diagnosis was 72 years, and nearly 89% of patients were at least 55 years of age when CLL was diagnosed.(33)

CLL is manifested by progressive accumulation of morphologically mature but immunologically less mature lymphocytes in the blood, bone marrow, and lymphatic tissues. The disease occurs in recognized phases that have been characterized by various clinical staging systems (Rai, Binet, etc.). The earliest stages are typically characterized by an asymptomatic indolent lymphocytosis, during which patients usually are not treated with specific therapy, but may require treatment for infectious, hemorrhagic, or immunologic complications.

Patients with symptomatic Rai Stage I or II CLL and patients with advanced disease (Rai Stage III or IV) generally are treated with chemotherapy. These patients commonly respond to initial therapy; however, the disease is characterized by periodic relapses during which patients become progressively less responsive.(34) Although allogeneic bone marrow transplantation has been employed in some patients, the method is highly toxic and generally not applicable to the older patients affected by this illness. Overall, the disease is generally regarded as incurable.

Patients with relapsed or refractory CLL are the focus of this NDA. These patients are quite different from patients with early-stage disease. In the advanced stages, patients are usually highly symptomatic, as evidenced by fever, night sweats, weight loss, generalized adenopathy, hepatosplenomegaly, and pancytopenia. Survival in the elderly population commonly affected by this disease tends to be short. Typically, death results as a direct consequence of disease (usually from infection or hemorrhage) rather than from other causes. Given the extensive amount of prior treatment, long-lived responses in patients with relapsed or refractory CLL are uncommon.

Chemotherapy for Relapsed or Refractory CLL

Despite undoubted therapeutic progress, a statistically significant improvement in survival in any stage of CLL has never been documented in any randomized trial. Nonetheless, new agents have resulted in improved response rates, and CLL is expected to follow all other forms of leukemia in which an increase in response (particularly CR) ultimately improves overall outcome.

In previously untreated patients, fludarabine has yielded significantly higher response rates than chlorambucil, CVP, and CHOP.(35,36,37) Several recent randomized trials have shown that the combination of fludarabine and cyclophosphamide produces higher response rates, including a significant improvement in CR, compared with single-agent fludarabine (see Table 4).(20,21,22,38,39)

Table 4: Major responses to initial therapy in previously untreated patients with CLL in recent, large, randomized trials

No. of patients (Investigators)	Chemotherapy	CR rate	Chemotherapy	CR rate
375 (Eichorst et al [20])	Fludarabine + cyclophosphamide	24%[a]	Fludarabine	7%
278 (Flinn et al [21])	Fludarabine + cyclophosphamide	22%	Fludarabine	6%
509 (Rai et al [22])	Fludarabine	20%	Chlorambucil	4%

Data from these trials are reported using standard NCI-WG criteria, which do not mandate use of CT/ultrasound imaging.(16)

[a] This trial incorporated CT imaging, which reduced the reported CR rate to 16% and 5%, respectively.

Although rituximab has shown little activity as a single agent, nonrandomized trials suggest that response rates to fludarabine with or without cyclophosphamide can be increased with the addition of rituximab in previously treated patients (see Executive Summary, Figure 5).(19) However, no data from a randomized trial that compares rituximab with other therapy have yet been reported.

The majority of previously untreated patients achieving CR exhibit evidence of minimal residual disease based on flow cytometry or RT-PCR.(40,41,42) This finding, in addition to the absence of a plateau in survival curves, continues to indicate that conventional treatments may not be curative.(14,36,37,43)

Very few randomized trials have been conducted in patients with relapsed or refractory CLL. In the United States, 2 drugs have been approved for this general indication: fludarabine (Fludara®) in 1991, based on 2 noncomparative studies, and alemtuzumab (Campath®) in 2001, based on 1 noncomparative study. An overview of the pivotal studies in these applications is provided in Table 5.

Table 5: Overview of pivotal studies in the NDAs for fludarabine and alemtuzumab

	Fludarabine (1991)[a]	Alemtuzumab (2001)[b]
Design	Single arm, Phase 1-2	Single arm, Phase 2
Efficacy		
No. of patients evaluated	79	93
CR	13%[c]	2%
PR	29%[c]	31%
Safety		
No. of patients evaluated	133	149
Died	22%[d]	10%[e]
Neutropenia (Grade 4)	59%[f]	37%[g]
Pneumonia	17%	15%

[a] Two studies (44)
[b] Single study for efficacy; 3 studies for safety (45)
[c] Determined based on criteria other than 1996 NCI-WG criteria (16)
[d] Identified as deaths "during study"; no further information available
[e] Deaths during treatment or within 30 days of last dose of study medication
[f] No G-CSF administered
[g] G-CSF administered to 35% of patients

Both agents were approved on the basis of noncomparative trials in which fewer than 100 patients participated and overall response (CR + nPR + PR) was the declared primary endpoint. Many of the responses (primarily PRs) in the alemtuzumab study were associated with clinical benefit (eg, symptomatic relief, reduction in splenomegaly) in a population declared to be "fludarabine-refractory." However, the duration of benefit was not specified. The median duration of overall response was 8.7 months.(46)

In the United States, patients who relapse from initial fludarabine-containing therapy are typically retreated with fludarabine administered either alone or in combination with other agents. Despite the availability of alemtuzumab, this agent is increasingly being used in a setting of minimal residual disease, because it appears to be much less effective in patients with bulky lymphadenopathy.(11,12,13) Both fludarabine and alemtuzumab are associated with substantial toxicity, which limits their use in a severely immuno-compromised population.

The combination of fludarabine and cyclophosphamide showed a high CR/nPR rate in early nonrandomized trials conducted in relapsed or refractory patients.(38,47,48) Accordingly, with the agreement of the FDA, this combination was selected as the control in the pivotal trial (GL303) in the Genasense CLL registration program. Notably, while this Phase 3 trial was underway, the FC

combination was unequivocally shown to be superior to fludarabine alone based on the CR rate in 2 large, multicenter, randomized clinical trials (see Table 4).(20,21) It should be noted, however, that both trials were conducted in previously untreated patients. Both randomized studies resulted in an overall response rate (CR + nPR + PR) that was approximately 50% lower than originally reported in the single-center, nonrandomized trial.(20,21,22).

In nonrandomized trials, FC has been tested both alone and in combination with rituximab (FCR) and mitoxantrone (FCM).(15,18,49) In other trials, pentostatin has been substituted for fludarabine. Consecutive, nonrandomized trials at M.D. Anderson Cancer Center in the relapsed/refractory CLL setting have demonstrated that FCR yielded approximately a two-fold increase in the incidence of CRs, compared with historical experience using FC alone.(15,18) However, time to progression and overall response were not different (see Executive Summary, Figure 5).(19)

Despite its regulatory approval, the role of alemtuzumab in the relapsed/refractory setting has not yet been clarified, largely due to its low activity in patients with bulky lymphadenopathy.(12,13) There is current interest in using alemtuzumab in patients with minimal residual disease after "debulking" with standard cytotoxic drugs such as FC.(11)

In summary, despite the myelosuppressive and immunosuppressive consequences of FC in a generally older patient population, this regimen represents an aggressive and commonly used standard of care in the United States, and randomized clinical trials have demonstrated the superiority of this regimen relative to fludarabine alone for inducing CR. No randomized trials have been reported that show superiority for any other regimen, except for Study GL303, the pivotal trial in the Genasense CLL NDA.

1.3 Regulatory History of Genasense in CLL

Key regulatory milestones pertinent to NDA 21-874 follow:

09 Jan 2002 — End-of-Phase 2 meeting: With respect to the primary endpoint, the FDA agrees that patients achieving CR or nPR will be considered as "responders" in the randomized Phase 3 study in CLL (GL303).

20 Jun 2003 — The FDA grants Fast Track designation for the review of Genasense in combination with fludarabine and cyclophosphamide for CLL, specifically noting that:

- CLL "is a serious, life-threatening disease complicated by an increased risk of infection, severe anemias and thrombocytopenias for which there is no cure for the majority of patients."

20 Jun 2003 (continued)	• the Sponsor's development program, including "the Randomized Study of Fludarabine and Cyclophosphamide With or Without Genasense in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (GL303) has the potential to address an unmet medical need."
15 Sep 2004	The FDA accepts the final statistical analysis plan for Study GL303.
30 Jun 2005	The Sponsor initiates the rolling submission of NDA 21-874.
28 Dec 2005	The Sponsor completes the submission of NDA 21-874.
28 Dec 2005	The Sponsor submits the protocol for the confirmatory study in CLL (GL305) to the FDA requesting a Special Protocol Assessment.
13 Mar 2006	The FDA files NDA 21-874 with a PDUFA decision date of 29 Oct 2006.
26 Jun 2006	The Sponsor receives approval from the FDA regarding the Special Protocol Assessment of confirmatory study GL305.
28 Jul 2006	The Sponsor initiates the confirmatory study GL305.

2. NONCLINICAL DATA

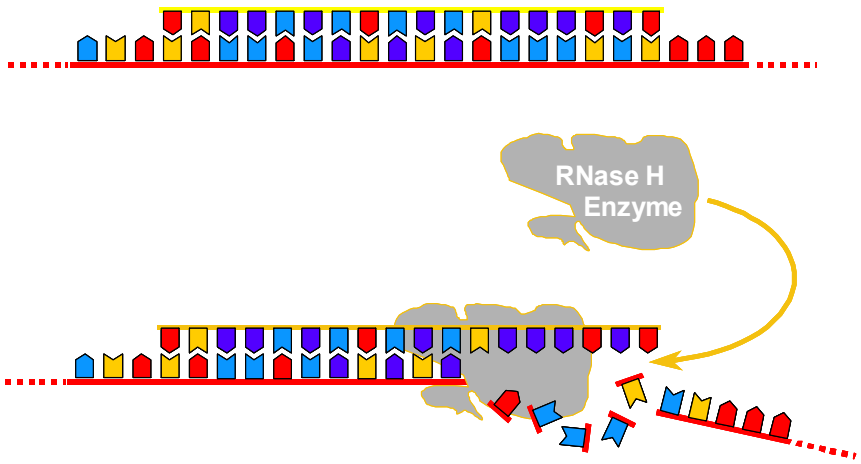
The nonclinical testing program included 32 pharmacology studies, 10 pharmacokinetics studies, 8 toxicokinetics studies, and 18 toxicology studies.

2.1 Nonclinical Pharmacology

Oblimersen (Genasense, oblimersen sodium) belongs to a class of drugs known as antisense. Antisense represents a pharmacologic mechanism for selectively reducing production of a specific protein.

Oblimersen, a synthetic, 18-base, single-stranded phosphorothioate DNA oligonucleotide, was selected for development from among 40 phosphorothioate DNA oligodeoxynucelotides in a screening process specifically designed to detect downregulation of *bcl-2* mRNA expression. Oblimersen selectively hybridizes to the first 6 codons (ie, 18 bases) of the mRNA open reading frame that encodes the Bcl-2 protein. As shown in Figure 7, formation of the mRNA/antisense duplex recruits an enzyme (RNase H) that degrades the mRNA strand and releases the antisense strand, allowing the drug to bind and cleave additional Bcl-2 mRNA molecules. Cleavage of the Bcl-2 mRNA eliminates the ability of the molecule to generate Bcl-2 protein.

Figure 7: Oligonucleotide/RNA-mediated cleavage by RNase H



The effects of oblimersen, alone and in combination with many cytotoxic drugs, have been assessed in a wide variety of cancer models.(50) The results have been broadly consistent: decreased expression of *bcl-2* mRNA and Bcl-2 protein, reduced cellular viability, increased apoptosis, reduction of tumor size, prolongation of survival in tumor-bearing animals treated with oblimersen plus chemotherapy, and synergistic cytotoxic activity with anticancer drugs.

2.2 Nonclinical Pharmacokinetics

The nonclinical pharmacokinetics program included 10 pharmacokinetics studies, with single dose (intravenous bolus and 24-hour intravenous infusion) studies in cynomolgus monkeys and repeated-dose (continuous intravenous infusion) toxicokinetics studies in rats, dogs, and cynomolgus monkeys.

Following a continuous intravenous infusion of oblimersen, steady-state plasma concentrations of oblimersen and the N-1 and N-2 active metabolites were achieved within 24 hours of the start of the infusion and are relatively consistent across species. There was no evidence of accumulation of the parent molecule or its metabolites after multiple dosing cycles. Plasma concentrations increased in a slightly more than dose-dependent manner. The pharmacokinetics of oblimersen in nonhuman primates and humans are similar, and nonclinical data provide a good prediction of pharmacokinetics in humans.

Following intravenous administration of ^{35}S-oblimersen to mice, radioactivity was rapidly and widely distributed into major organs. The kidneys and liver exhibited the highest concentrations of radioactivity, followed by the spleen. Significant amounts of radioactivity were also found in the bone marrow. No oblimersen was detected in the brain. The distribution characteristics observed for oblimersen were similar to those reported for other phosphorothioate oligonucleotides in mice, rats, and monkeys, where rapid clearance of phosphorothioate oligonucleotides from plasma occurs with concomitant appearance in tissues; the highest concentrations in all species were found in the kidneys, liver, spleen, and lymph nodes.

Oblimersen is highly protein bound in the plasma of rats, monkeys, and humans; the in vitro plasma protein binding of oblimersen was > 99%, a level similar to other phosphorothioates. The principal in vivo metabolites of oblimersen (18 nucleotides in length) are rapidly formed by sequential removal of nucleotides by ubiquitous cellular and extracellular endonucleases and exonucleases to form shortened oligonucleotide species. Thus, N-1 and N-2 metabolites are 17 and 16 nucleotides in length, respectively. The exposure to oblimersen and the N-1 and N-2 metabolites in humans and the pivotal toxicology species (ie, cynomolgus monkey) was qualitatively and proportionally similar. The N-1 and N-2 oligonucleotides have been shown to have activity in cell-free and cell-culture models.

Urinary and fecal excretion represented minor pathways for elimination of the parent compound following intravenous bolus administration of ^{35}S-oblimersen in mice. The high levels of radioactivity excreted in the urine and feces in this study were probably related to shorter nucleotide metabolites or the free radiolabel.

2.3 Toxicology

The nonclinical toxicology program included repeated-dose toxicity studies in rodents, dogs, and monkeys and single-dose studies in monkeys. The repeated-dose toxicity studies lasted for up to 1 month (up to 2 cycles) in dogs and up to 6 months (up to 8 cycles) in both rats and monkeys. Each cycle consisted of continuous intravenous infusion of oblimersen for 7 days followed by a 2-week washout period. A battery of genotoxicity studies and Segment II reproductive toxicity studies in rats and rabbits were performed. Toxicity studies were supported by concurrent toxicokinetic analyses. In addition, oblimersen was also evaluated in mice and monkeys by the subcutaneous route for 2 weeks. Overall, the program included 18 studies.

Single-dose intravenous toxicity was assessed in a dose-ranging study in cynomolgus monkeys using intravenous bolus doses up to 24 mg/kg and a single intravenous bolus or 24-hour continuous intravenous infusion of 30 mg/kg in a safety pharmacology study and using a single intravenous bolus of 3 or 7 mg/kg in a pharmacokinetic study. Repeated-dose toxicity was assessed in monkeys (7-day or 2-cycle, 7-day intravenous infusion at doses of 1.75, 7, 28, and 56 mg/kg/d and a 24-week (8-cycle) infusion study at doses of 1, 7, and 28 mg/kg/d.

In all repeated-dose toxicity studies, the toxicity profile was consistent with the expected class toxicities of phosphorothioate oligonucleotides. These included proliferation of reactive sinusoidal lining cells of the liver, multifocal single cell necrosis of hepatocytes, and, primarily at higher doses, prolonged activated partial thromboplastin time (APTT).

Dose-related toxicities observed following oblimersen administration as a single intravenous bolus or 24-hour intravenous infusion in monkeys included increased APTT, activation of the alternative complement pathway (only in animals receiving intravenous bolus injections), and alterations in biochemical parameters suggesting treatment-related hepatocellular damage or some striated muscle tissue involvement.

Serious outcomes, including deaths of monkeys receiving oligonucleotides as rapid intravenous bolus doses, have been reported previously (51) and have been discussed extensively in the published literature as an expected class effect (52). A single monkey died after administration of a rapid intravenous bolus of Genasense 7 mg/kg in a pharmacokinetic study.

Non-specific immune effects were also consistent with the expected class effects and included infiltration of tissues with mononuclear cells, splenomegaly (ie, white pulp hyperplasia), and lymph node enlargement with histiocytosis and/or hyperplasia. Immune stimulation also resulted in severe effects at the infusion site, where thickening and masses eventually prevented infusion of test article into

some animals. The inflammation seen at the infusion site indicated a correlative increase in inflammation in many tissues.

Oblimersen was not teratogenic in developmental toxicology studies conducted in rats and rabbits. At doses higher than 0.1 mg/kg/d (rats) and 3 mg/kg/d (rabbits), maternal toxicity was associated with post-implantation loss, fetal ossification delays in rats and fetal weight reduction in rabbits.

The class of phosphorothioate oligodeoxynucleotides presents a common profile of toxic effects in rodents and monkeys, which is sequence-independent. Briefly, this profile consists of increased coagulation time, complement activation, uptake of oblimersen in kidney and liver resulting in histopathologic changes in kidneys (including tubular nephropathy, and glomerulopathy in monkeys) and liver (including Kupffer cell activation), and immune stimulation, including splenomegaly, lymphoid hyperplasia, and mononuclear cell infiltration in many tissues.

Overall, the nonclinical toxicology data present a safety profile for oblimersen consistent with the profile of phosphorothioate oligonucleotides as a class and acceptable in humans at the dosage proposed for the indication.

3. CLINICAL PHARMACOLOGY

3.1 Pharmacokinetics

The clinical pharmacokinetics of oblimersen and its metabolites, N-1 and N-2, were investigated in 3 primary studies and 7 supportive studies. In the 3 primary studies, pharmacokinetics were assessed in:

- patients with relapsed or refractory CLL who received oblimersen 3 to 7 mg/kg/d by 5-day (Cycle 1) or 7-day (Cycles 2+) continuous intravenous infusion as a single agent (Study GL208)
- patients with advanced melanoma who received Genasense 7 mg/kg/d by 7-day continuous intravenous infusion and dacarbazine 1000 mg/m^2 intravenous over a 60-minute period beginning 120 hours after the start of the Genasense infusion (Study GPK101)
- patients with hormone-refractory prostate cancer who received Genasense 7 mg/kg/d by 5-day continuous intravenous infusion and docetaxel 75 mg/m^2 over a 60-minute period on Day 4 of the Genasense infusion (Study GP202 Phase 2B).

The pharmacokinetics profile of oblimersen is consistent with that of agents in its class (see Table 6). Steady-state plasma drug concentrations are rapidly achieved (ie, within 10 hours). The drug is rapidly metabolized to its N-1 and N-2 metabolites and rapidly cleared from the blood ($t_{1/2}$ ~ 2.4 hours). Excretion of intact oblimersen in the urine is minimal, and the drug is highly protein bound.

Table 6: Summary of pharmacokinetic findings (mean oblimersen values) by primary pharmacokinetic study

Study	Regimen	Dose (mg/kg/d)	Cycle	C_{ss} (μg/mL)	CL (L/h/kg)	Cl_{renal} (L/h)	$t_{1/2}$ (h)	V_z (L/kg)
GL208	Genasense 5-day intravenous infusion	3	1	1.68[a]	0.16	0.061	NR	NR
		4	1	1.16	0.15	0.044	NR	NR
GPK101	Genasense 7-day intravenous infusion and dacarbazine 1000 mg/m^2 on Day 5	7	1	3.15	0.09	0.058	2.4	0.281
GP202 Phase 2B	Genasense 5-day intravenous infusion and docetaxel 75 mg/m^2 on Day 4	7	1	3.48	0.09	NR	NR	NR
		7	4	3.66	0.09	NR	NR	NR

CL = clearance; C_{ss} = concentration at steady state; NR = not reported; $t_{1/2}$ = half-life; V_z = volume of distribution

[a] The mean value includes the data of 1 patient who had an outlier value at 120 hours; the median C_{ss} was 0.824 μg/mL.

Examination of the dose proportionality of oblimersen exposure was assessed in 61 patients in 2 of the primary pharmacokinetic studies (GL208 and GPK101). Across the range of doses studied (3 to 7 mg/kg/d), correlation of steady-state plasma oblimersen concentration with daily dose was consistent with linear pharmacokinetic behavior. Although not designed to assess the effects of age or gender on oblimersen exposure, a pooled exploratory analysis of data in these 2 studies suggested that neither gender nor age (range, 26 to 76 years) had any effect on oblimersen exposure.

In Study GL208, the mean total clearance of oblimersen was estimated to be 0.16 and 0.15 L/h/kg for the 3 and 4 mg/kg/d dose groups, respectively. In Study GP202 Phase 2B (oblimersen 7 mg/kg/d), the mean total clearance of intact oblimersen was the same in Cycles 1 and 4 (0.09 L/h/kg). Comparable mean total plasma clearance (0.09 L/h/kg) was observed in Study GPK101 (oblimersen 7 mg/kg/d). The mean half-lives of the N-1 metabolite (2.3 hours) and Genasense (2.4 hours) were similar; there were insufficient data to calculate the half-life for the N-2 metabolite. The exposure (based on C_{ss}) of patients to the N-1 and N-2 metabolites was approximately 38% to 50% and 13% to 38%, respectively, of the exposure to oblimersen in the 3 primary pharmacokinetic studies.

The estimated mean volume of distribution (V_z) for oblimersen was 0.281 L/kg in the Study GPK101 (oblimersen 7 mg/kg/d). These results suggest that oblimersen distributed to a volume of approximately 20 L for an average (70 kg) individual, consistent with the distribution of other phosphorothioate oligonucleotides.

Urinary excretion and renal clearance of oblimersen and its N-1 and N-2 metabolites were determined in Studies GL208 and GPK101. In Study GL208, renal clearance of intact oblimersen for the 3 mg/kg/d and 4 mg/kg/d dose groups was 0.061 L/h and 0.044 L/h, respectively. Comparable mean renal clearance (0.058 L/h) of intact oblimersen was observed in Study GPK101 (oblimersen 7 mg/kg/d). Renal clearance of the N-1 and N-2 metabolites in Study GL208 was 0.128 L/h and 0.177 L/h, respectively. Comparable mean renal clearance of N-1 was observed in Study GPK101 (0.164 L/h). The mean renal clearance of the N-2 metabolite estimated in Study GPK101 was 0.378 L/h. These results indicate that renal clearance represents only a small portion of the plasma clearance (approximately 10 to 11 L/h for a 70-kg individual) for intact oblimersen, consistent with reports for other phosphorothioate oligonucleotides.(53,54,55)

3.2 Pharmacokinetic/pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic relationships were assessed in 3 NCI-sponsored studies. The first study explored oblimersen pharmacokinetic/ pharmacodynamic and clinical activity in patients with relapsed or refractory acute myelogenous leukemia receiving Genasense (4 or 7 mg/kg/d) as a 9-day continuous intravenous infusion, with fludarabine, cytarabine, and G-CSF (FLAG) salvage chemotherapy starting on Day 6 of the infusion.(56) Plasma pharmacokinetics showed that oblimersen plasma C_{ss}, AUC, and CL values were

consistent with linear pharmacokinetics. Relative differences between pretreatment and Day 5 (prior to salvage chemotherapy) levels of *bcl-2* mRNA transcripts were measured in bone marrow aspirates from 12 patients. Of the 12 samples, 9 showed downregulation of *bcl-2* mRNA.

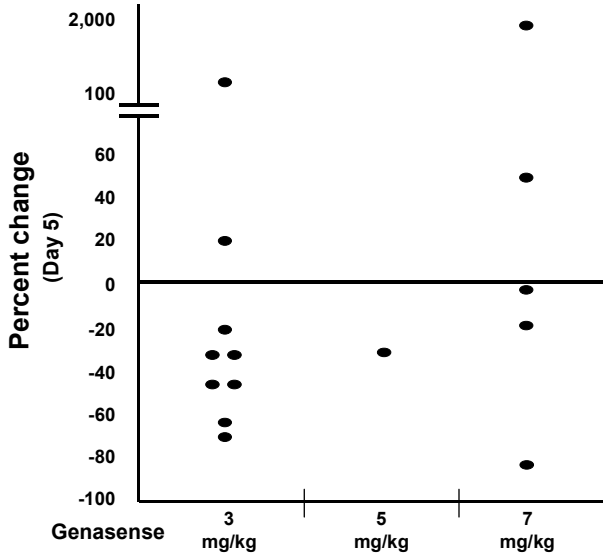
A hybridization-based ELISA assay for oblimersen was used to analyze retained samples from this trial for oligonucleotide uptake.(57) Bone marrow samples and peripheral blood mononuclear cells were available from 8 patients, including 5 patients treated with Genasense at 4 mg/kg/d and 3 patients treated with Genasense at 7 mg/kg/d and were used for determination of intracellular oblimersen levels and *bcl-2* mRNA levels. Samples collected after 72 and 120 hours of Genasense exposure showed intracellular uptake of oblimersen in mononuclear cells from both marrow (3.4 to 40.6 pmol/mg protein) and blood (0.47 to 19.4 pmol/mg protein). Samples from half of the patients showed downregulation of *bcl-2* mRNA in bone marrow, 2 showed increased *bcl*-2 mRNA, and the remaining 2 were unchanged.

The second study assessed the relationship between clinical response, plasma and intracellular oblimersen concentrations, and changes in *bcl-2* mRNA and protein levels in bone marrow mononuclear cells in 29 elderly patients receiving Genasense in combination with chemotherapy for previously untreated acute myelogenous leukemia.(58) Mean C_{ss} oblimersen values were consistent with those previously reported with 7 mg/kg/d infusions. Bone marrow and plasma samples collected before treatment and after 72 hours of Genasense infusion prior to initiation of chemotherapy were analyzed for plasma and intracellular oblimersen concentrations using the hybridization-ELISA method. Lysates from bone marrow mononuclear cells were assayed for Bcl-2 protein levels by ELISA and for *bcl-2* mRNA levels by RT-PCR.

Following 72 hours of exposure to oblimersen, patients achieving a complete response showed decreases of the median *bcl-2* mRNA and protein levels relative to baseline. These preliminary results suggest a correlation between clinical outcome and the antisense activity of Genasense as measured by *bcl-2* mRNA and protein downregulation.

A third, unpublished study evaluated 7 days of oblimersen administration at 3, 5 and 7 mg/kg every 21 days in pediatric patients with solid tumors (Rheingold et al, submitted). Peripheral blood mononuclear cells were assayed for Bcl-2 protein levels as a function of oblimersen dose. Bcl-2 protein levels were reduced by Day 5 of Genasense administration in 10 of 15 patients, including 7 of 9 patients treated at 3 mg/kg/d, as shown in Figure 8.

Figure 8: Bcl-2 response in peripheral blood mononuclear cells by Genasense dose: Change from baseline (Day 0) on Day 5 (Adapted from Rheingold et al, submitted [M Hogarty Laboratory; COG-ADVL0211 Study])



These preliminary clinical measurements show uptake of oblimersen into patient cells and downregulation of Bcl-2 at the level of both mRNA and protein. Work is ongoing to expand these analyses into additional patient populations and tumor cell types.

3.3 Metabolism-based Drug-drug Interaction Studies

Metabolism-based drug-drug interactions are not likely with the Genasense dose and regimen proposed based on findings from in vitro studies, including:

- 3 studies that examined oblimersen for direct metabolism-dependent inhibition of CYP450 isozymes in human liver microsomes. Results showed no significant inhibition by oblimersen with the possible exception of inhibition of CYP1A2. The K_i for CYP1A2 was determined to be 6.0 μM. However, at clinically relevant oblimersen concentrations, the possibility of drug-drug interactions for drugs metabolized by CYP450 1A2 isozymes is considered remote (based upon the ratio of C_{ss} to K_i of < 0.1).(59)
- 2 studies that examined oblimersen induction of CYP450 isozymes in cultured or cryopreserved human hepatocytes. Results showed no significant induction of any CYP450 isozymes tested.

No formal human or animal in vivo drug-drug interaction studies have been performed.

3.4 Plasma Protein Binding

Phosphorothioate oligonucleotides generally are highly (91% to 99%) protein bound, primarily to albumin and α2-macroglobulin.(60). Consistent with its class, oblimersen was found to be highly protein bound in human plasma (99.60 ± 0.31%), as assessed by ultrafiltration.

3.5 Special Populations

Studies in patients with renal impairment and hepatic impairment are ongoing (Study GPK104, "A Phase I Pharmacokinetic Study of Genasense in Patients with Normal and Mildly to Moderately Impaired Renal Function," and Study GPK103, "A Pharmacokinetic Study of Genasense [Bcl-2 Antisense Oligonucleotide] in Combination with Dacarbazine [DTIC] in Patients with Advanced Melanoma and Normal or Impaired Hepatic Function"). The protocol for the study in patients with hepatic impairment was reviewed by the FDA as a Special Protocol Assessment.

Preliminary results available in the hepatic impairment study for 3 patients (2 with normal hepatic function and 1 with moderately impaired hepatic function [ie, Child-Pugh Classification B]) suggest there was no change in oblimersen clearance or metabolism in the 1 patient with impaired hepatic function.

3.6 Dose Selection

The Phase 1-2 study of Genasense monotherapy in patients with relapsed or refractory CLL (Study GL208) showed that 3 mg/kg/d was the maximally tolerated dose. Two patients treated with Genasense for 5 to 7 days achieved a PR, and other evidence of clinical activity, including disappearance or reduction in hepatosplenomegaly and lymphadenopathy and improvement in absolute lymphocyte counts, was apparent (see Section 4.2.3 and Table 8).

The short plasma half-life of oblimersen and the relatively long half-life of Bcl-2 protein in tumor cells provide the rationale for administration of oblimersen by continuous intravenous infusion. The extent of downregulation of Bcl-2 after 14 days of Genasense was not superior to that observed after 5 days of Genasense administration. These and other data suggest that maximal downregulation of Bcl-2 is achievable with infusions of Genasense as short as 5 days. A 7-day infusion was evaluated in the Genasense pivotal study in CLL (GL303) because the associated chemotherapy is given daily for 3 days. To ensure continued suppression of Bcl-2 levels during chemotherapy, the clinical schedule was 4 days of Genasense alone, followed by 3 days of Genasense plus FC. In particular, in the Genasense arm, patients received fludarabine 25 mg/m^2/d intravenously followed by cyclophosphamide 250 mg/m^2/d intravenously on Days 5, 6, and 7 of the Genasense infusion.

4. EFFICACY IN RELAPSED OR REFRACTORY CLL

4.1 Clinical Development Program in CLL

At the time the NDA was filed, the Sponsor's clinical development program in CLL included 3 studies:

- a completed Phase 1-2 dose-finding study (GL208) in 40 patients with relapsed or refractory CLL who were treated with single-agent Genasense
- an ongoing Phase 2 study (GL217) in 24 patients, including 19 patients with relapsed or refractory CLL and 5 previously untreated patients, who were treated with Genasense plus fludarabine and rituximab (61)
- a completed randomized, active-control Phase 3 study (GL303) in 241 patients with relapsed or refractory CLL who were treated with Genasense plus standard chemotherapy (FC) or standard chemotherapy (FC) alone

4.2 Phase 1-2 Study: Genasense Monotherapy (GL208)

A Phase 1-2, multicenter, open-label study (GL208) was conducted to determine the maximum tolerated dose of Genasense in patients with relapsed or refractory CLL who had failed or were resistant to regimens containing fludarabine, as well as to assess the efficacy of Genasense when administered to this patient population at the maximum tolerated dose identified in Phase 1 and to evaluate the pharmacokinetics of oblimersen administered by 5- and 7-day continuous intravenous infusion.

4.2.1 Methods

In both Phase 1 and Phase 2, initial treatment with Genasense consisted of a 5-day period of therapy. After a 2-week observation period (on or about Day 21 of the cycle), treatment resumed with a 7-day period of therapy followed by another 2-week observation period. Patients whose disease was at least stable after the initial 2 cycles of Genasense therapy were permitted to be treated with up to 4 additional cycles of the drug at the same daily dose as the immediately preceding cycle. This treatment could be continued for up to 12 cycles, if a patient appeared to have an objective response (ie, CR, nPR, or PR).

Key inclusion criteria included relapsed or refractory symptomatic and measurable CLL (based on the NCI-WG guidelines) for which therapy was required and at least 1 prior chemotherapy regimen that contained a purine analog.(16) Other inclusion criteria were age ≥ 18 years and an ECOG Performance Status of 0, 1, or 2.

Patients were formally evaluated for response utilizing the revised NCI-WG guidelines after the first 2 cycles of treatment and at least once again at either the

time of maximum response or upon completion of 6 cycles of treatment, and/or study completion. Additional assessments included evaluation of splenomegaly, hepatomegaly, lymphadenopathy, absolute lymphocyte count, and ECOG Performance Status.

4.2.2 Study Population

A total of 40 patients were enrolled in this noncomparative study. The study population consisted predominantly of Caucasian males (see Table 7). About two thirds of all patients were Rai Stage II-III. The mean time since CLL diagnosis was 5.5 years for patients in Phase 1 and 3.5 years for patients in Phase 2. All patients had relapsed or refractory disease and were heavily pretreated with a mean of 3.5 prior chemotherapy regimens.

CLL findings at baseline included splenomegaly in 17 patients, hepatomegaly in 7 patients, and lymphadenopathy and absolute lymphocyte count > 5,000/μL in 22 patients each.

Table 7: Demographics and baseline characteristics: ITT Population (Study GL208)

	Genasense		
	Phase 1 (N=14)	**Phase 2 (N=26)**	**Overall (N=40)**
Gender, n (%)			
Male	9 (64)	17 (65)	26 (65)
Female	5 (36)	9 (35)	14 (35)
Race, n (%)			
Caucasian	12 (86)	26 (100)	38 (95)
Hispanic	1 (7)	0	1 (2.5)
Black	1 (7)	0	1 (2.5)
Age, years			
Mean (SD)	61.0 (5.91)	57.2 (7.96)	58.5 (7.46)
Median	60.0	55.5	58.5
Minimum, maximum	54.0, 72.0	43.0, 70.0	43.0, 72.0
Rai stage at baseline, n (%)			
I	2 (14)	0	2 (5)
II	3 (21)	14 (54)	17 (42.5)
III	5 (36)	5 (19)	10 (25)
IV	2 (14)	7 (27)	9 (22.5)
Richter's transformation	2 (14)	0	2 (5)
CLL history, time since diagnosis, years[a]			
Mean (SD)	5.5 (3.88)	3.5 (3.40)	4.2 (3.67)
Median	3.9	1.9	3.3
Minimum, maximum	0.8, 13.1	0.1, 12.9	0.1, 13.1
Number of prior chemotherapy regimens			
Mean (SD)	3.9 (2.50)	3.3 (1.87)	3.5 (2.10)
Median	3.5	3.0	3.0
Minimum, maximum	1.0, 10.0	1.0, 10.0	1.0, 10.0

SD = standard deviation
[a] This information was not recorded for 1 patient.

Most patients received at least 2 cycles of treatment. Patients who began treatment with 5 mg/kg/d or 7 mg/kg/d did not progress beyond the first cycle due to toxicity. A total of 9 patients completed 6 cycles of treatment, of which 8 patients were treated in Phase 2 at 3 mg/kg/d and 1 patient began treatment in Phase 1 at a dose of 4 mg/kg/d. The maximum number of cycles a patient received was 8.

The most common reasons for discontinuation from Phase 1 were adverse events and lack of efficacy (each 29%). In Phase 2, most patients discontinued due to progressive disease (42%).

4.2.3 Efficacy Findings

Response Rate

The best clinical response was a PR that occurred in 2/26 (8%) patients:

- One patient treated with 4 prior chemotherapy regimens had a PR after receiving 2 cycles. At Cycle 6, the patient had stable disease, and disease progression occurred by Cycle 7.
- One patient treated with 5 prior chemotherapy regimens had a PR after receiving 2 cycles. Disease progression occurred by Cycle 6. It is noteworthy that this patient had a history of Richter's transformation.

Of the remaining 24 patients, 12 had stable disease and 12 had progressive disease.

Additional evidence of single-agent Genasense activity was apparent based on changes in splenomegaly, hepatomegaly, lymphadenopathy, and absolute lymphocyte count (see Table 8). Notably,

- complete disappearance of splenomegaly was observed in 2/17 patients (12%) with this finding at baseline
- a ≥ 50% reduction from baseline in lymph node size was observed in 7/22 patients (32%) with lymphadenopathy at baseline
- a ≥ 50% reduction from baseline in absolute lymphocyte count was observed in 11/22 patients (50%) with an absolute lymphocyte count > 5,000/μL at baseline

Table 8: Genasense monotherapy in CLL: Additional evidence of activity among patients with specific finding at baseline (Study GL208)

Clinical activity	n/N (%)
Splenomegaly	
At least a 50% reduction	7/17 (41)
Complete disappearance	2/17 (12)
Lymphadenopathy	
At least a 25% reduction	10/22 (45.5)
At least a 50% reduction	7/22 (32)
Lymphocytosis > 5,000/μL	
At least a 25% reduction	17/22 (77)
At least a 50% reduction	11/22 (50)
Normalization	5/22 (23)

Patients are counted in all applicable categories.

Efficacy Conclusions

Single-agent Genasense demonstrated limited but measurable activity, including PR in 2 heavily pretreated patients after 2 cycles of Genasense.

Other efficacy evaluations, including disappearance or reduction in splenomegaly, hepatomegaly, and lymphadenopathy, and normalization or reduction of absolute lymphocyte count, supported the clinical benefit of Genasense in these relapsed or refractory CLL patients.

4.3 Randomized Phase 3 Study: Genasense in Combination with FC (GL303)

A randomized, multicenter, open-label, parallel-group Phase 3 study (GL303) was conducted to compare the efficacy and safety of Genasense in combination with FC vs. FC alone in patients with relapsed or refractory CLL, as demonstrated by treatment failure after ≥ 1 regimen and a minimum of 2 prior cycles of a fludarabine-based regimen. This trial employed a definition of "refractory" that was used in the pivotal trial for alemtuzumab, as follows:(46)

- A patient was considered to be refractory if he/she had failed to achieve at least a PR, or disease had recurred within 6 months of treatment.
- A patient was considered to have relapsed if he/she had recurrence of disease after achieving a PR that had lasted ≥ 6 months.

The primary efficacy endpoint was the proportion of patients treated with FC vs. FC combined with Genasense who achieved CR or nPR.

Secondary efficacy endpoints were duration of response, overall response rate (CR + nPR + PR), time to progression, clinical benefit, and survival.

4.3.1 Methods

Eligible patients were stratified according to the following criteria:

- Responsive to prior treatment with a fludarabine-containing regimen vs. refractory to prior treatment with a fludarabine-containing regimen
- 1 to 2 prior treatment regimens vs. 3 or more prior treatment regimens
- > 6-month response to last prior therapy vs. ≤ 6-month response to last prior therapy

Patients were then randomly assigned in a 1:1 ratio to receive GFC or FC alone. In the GFC group, patients received Genasense 3 mg/kg/d as a continuous intravenous infusion on Days 1 through 7 and fludarabine 25 mg/m^2/d intravenously over 20 to 30 minutes, followed by cyclophosphamide 250 mg/m^2/d intravenously over 30 to 60 minutes on Days 5, 6, and 7. The same FC regimen alone was administered on Days 1 through 3 in the FC group.

The dose of Genasense was not to be modified; however, treatment could be delayed according to protocol-specified guidelines. Fludarabine and cyclophosphamide doses could be reduced or delayed according to protocol-specified guidelines.

All patients received allopurinol, sulfamethoxazole-trimethoprim (or dapsone, aerosolized or intravenous pentamidine, or atovaquone suspension if a patient could not tolerate sulfamethoxazole-trimethoprim), acyclovir (or other similar agents), and filgrastim. Erythropoietin was also recommended, as well as 5-hydroxytryptamine antiemetics (or the equivalent) prior to treatment with FC. Prophylactic use of corticosteroid medications as antiemetics was not permitted.

Administration of study medication was to be repeated every 28 days for a maximum of 6 cycles until disease progression or the occurrence of toxicity necessitating discontinuation of treatment. Patients who achieved a complete response could discontinue treatment at the discretion of the investigator after response was confirmed by bone marrow examination.

4.3.1.1 Entry Criteria

Key inclusion criteria included the following:

1. Relapsed or refractory CLL after at least 2 cycles of a fludarabine-containing regimen:
   a. Relapsed – relapse after having achieved a response (ie, post remission or post plateau) on or off therapy
   b. Refractory – progressive disease without response for at least 6 months after administration of at least 2 cycles of myelosuppressive chemotherapy
2. Measurable disease established by the revised guidelines of the NCI-WG for the diagnosis of CLL (16)
3. Intermediate or high-risk CLL (Modified Rai Stage); patients with intermediate-risk disease must have satisfied at least 1 of the following criteria for active disease:
   a. Massive or progressive splenomegaly and/or lymphadenopathy (massive splenomegaly was defined by spleen tip > 6 cm below costal margin)
   b. Presence of weight loss > 10% over the 6-month period preceding enrollment in this study; Grade 2 or 3 fatigue
   c. Fevers > 100.5°F or night sweats for > 2 weeks without evidence of infection
   d. Progressive lymphocytosis with an increase of > 50% over a 2-month period or an anticipated doubling time of less than 6 months
   e. Worsening anemia or thrombocytopenia
4. ECOG Performance Status of 0, 1, or 2
5. Adequate organ function determined within 2 weeks prior to randomization

Key exclusion criteria included the following:

1. Rai Stage 0 disease, or stable disease not requiring therapy
2. Concurrent medical disease that precluded safe delivery of experimental treatment
3. Prior major surgery or other therapy for CLL, including radiation therapy, immunotherapy, and cytokine, biologic, or vaccine therapy, within 3 weeks prior to enrollment, or failure to recover from any serious adverse effects of such therapies
4. Prior organ allograft or autologous or allogeneic stem cell transplant
5. Concurrent investigational or corticosteroid therapy

6. Secondary leukemia or history of antecedent hematologic disorder prior to initial onset of CLL (eg, myelodysplasia)
7. Concomitant anticoagulant therapy with the exception of warfarin 1 mg/d for central line prophylaxis

4.3.1.2 Efficacy Assessments

The following assessments were performed in each cycle during protocol therapy, as well as 1 month after ending protocol therapy and every 2 months in the follow-up period for up to 36 months from the date of randomization,

- a physical examination, including measurement of the liver, spleen, and lymph nodes
- disease-related symptoms
- a complete blood count, including differential

At the end of protocol therapy, re-evaluation by CT/ultrasound also was required for all patients with a baseline abnormality on CT/ultrasound.

When all patients had been followed for at least 6 months after ending protocol therapy, Dr G Threatte, an independent hematopathologist, determined response based on bone marrow specimens and Dr K Rai, an external clinical expert, determined clinical response and date of progression. In particular:

- Dr Threatte was blinded to study treatment, as well as information about the patient's clinical condition. For patients who had a potential CR based on peripheral blood counts and clinical criteria, he evaluated a bone marrow specimen. A bone marrow reading of CR or nPR by Dr Threatte was necessary but not sufficient for a patient's response to be called a CR or an nPR.
- Dr Rai was blinded to study treatment. He assessed clinical response according to the revised guidelines of the NCI-WG (see Appendix, Section 1).(16) These guidelines do not require CT/ultrasound imaging, but advise that they may be performed at the investigator's discretion. For all patients, Dr Rai reviewed peripheral blood counts, physical examination and B symptom [night sweats and fevers] findings, and CT/ultrasound reports and the bone marrow assessment by Dr. Threatte to determine clinical response and the date of disease progression. Dr. Rai's determinations of response and date of progression were used in all efficacy analyses.

A CR/nPR required that all criteria be met for a period of 2 months and into the follow-up period and was defined by clinical, hematologic, and bone marrow findings.(16) In particular, bone marrow aspirate or biopsy were required when clinical and peripheral hematologic criteria consistent with CR were demonstrated. As specified in the protocol, in patients with an abnormality on

CT/ultrasound at baseline, postbaseline results had to be negative (ie, < 1.5 cm in both dimensions based on lymphoma guidelines) to confirm CR.(62)

A patient was considered to have an nPR if he/she had a CR by all criteria except for persistent lymphoid nodules in bone marrow. A patient was considered to have stable disease if he/she did not fulfill the criteria for complete response or partial response, but did not exhibit progressive disease.

4.3.1.3 Statistical Considerations

Based upon the published literature at the time the study was designed, it was assumed that the response rate (CR + nPR) would be 24% for the FC group vs. 44% for the GFC group (ie, a proportional incremental improvement of 80%). A minimum of 200 patients (100 per treatment arm) was needed to provide a power of 80% at an overall alpha of 0.05 (two-sided), accounting for the interim analysis using a Chi-Square test.

As specified in the protocol, an interim analysis was to be performed after approximately half of the planned number of patients had been followed for at least 6 months to assess (1) the feasibility of continued development of Genasense in this indication and (2) whether the planned sample size was adequate. This interim analysis was performed on the first 100 patients randomized with at least 6 months of follow-up from the date of randomization. Observed rates of CR + nPR were compared between the 2 treatment groups using the continuity-corrected Pearson Chi-Square test. At that time, it was decided that sample size would not be increased. Based on the Lan and DeMets alpha-spending approach for the O'Brien and Fleming decision rule, the interim alpha for the primary efficacy analysis should be 0.001 and the final primary analysis used an adjusted nominal alpha of 0.049.

The following efficacy endpoints were analyzed:

Response Rate: the proportion of patients identified by the blinded external clinical expert as having CR or nPR

Overall Response Rate: the proportion of patients identified by the blinded external clinical expert as having CR or nPR or PR

Duration of Response (CR + nPR and CR + nPR + PR): the date when clinical response criteria were first met to the earliest date when either progressive disease was determined by the blinded external clinical expert or other CLL therapy was initiated

Time to Progression: the date of randomization to the date of progressive disease determined by the blinded external clinical expert prior to the use of other CLL therapy

Clinical Benefit: resolution of B symptoms (night sweats and fever); resolution or reduction of massive splenomegaly; improvement in ECOG Performance Status, disease-related anemia, and fatigue; decreased use of RBC transfusions and dose of erythropoietin; resolution of other disease-related symptoms (ie, early satiety and abdominal discomfort due to hepatosplenomegaly and impaired cosmesis and impaired mobility due to lymphadenopathy)

Survival: the date of randomization to the date of death

Details of the statistical analyses performed are included in the Appendix (see Section 2). For assessments related to response rate, only data through the cutoff date of 01 Sep 2004 prior to unblinding of the study were included in analyses, as specified in the statistical analysis plan. For secondary efficacy endpoints of duration of response, time to progression, and clinical benefit , data through Jun 2005 when all patients had been followed for a minimum of 24 months from the date of randomization were included in analyses.

4.3.2 Study Population

A total of 223 study sites were initiated; 241 patients were randomized at 100 sites in 8 countries (GFC group, 120 patients; FC group, 121 patients). Approximately 60% of patients were enrolled at study sites in the United States. A majority of patients enrolled in both groups were Caucasian men and less than 65 years of age (see Table 9).

Table 9: Demographic characteristics by treatment group: ITT Population (Study GL303)

Demographic characteristic	GFC (N = 120)	FC (N = 121)
Age, years		
Mean (SD)	62.5 (10.17)	62.0 (9.13)
Median	62.5	63.0
Minimum, maximum	35, 86	42, 82
Age group, n (%)		
< 65 years	67 (55.8)	69 (57.0)
≥ 65 years	53 (44.2)	52 (43.0)
≥ 75 years	17 (14.2)	10 (8.3)
Gender, n (%)		
Male	89 (74.2)	89 (73.6)
Female	31 (25.8)	32 (26.4)
Race, n (%)		
White, not of Hispanic origin	105 (87.5)	109 (90.1)
Black, not of Hispanic origin	6 (5.0)	7 (5.8)
Hispanic	8 (6.7)	4 (3.3)
Other[a]	1 (0.8)	1 (0.8)

N (total number of patients in the group) = denominator for percentage; SD = standard deviation

[a] Includes 1 patient with race recorded as Native South American and 1 patient with race recorded as American Indian or Alaskan Native

Patients in the ITT Population had similar disease stage and CLL immunophenotype at baseline (see Table 10). The largest percentage of patients had Modified Rai Stage IV disease (GFC group, 35%; FC group, 36%). Patients in the GFC group had CLL for approximately 1 year longer (from date of initial diagnosis to date of randomization) than those in the FC group (median: GFC group, 70.2 months; FC group, 58.1 months).

Table 10: CLL history by treatment group: ITT Population (Study GL303)

Characteristic	GFC (N = 120)	FC (N = 121)
Time from initial diagnosis to randomization, months		
Mean (SD)	78.8 (56.5)	69.3 (51.5)
Median	70.2	58.1
Minimum, maximum	2.4, 383.8	2.2, 249.6
Modified Rai Stage, n (%)		
0	0 (0)	1 (1)
I	29 (24)	28 (23)
II	37 (31)	30 (25)
III	12 (10)	17 (14)
IV	42 (35)	44 (36)
Unknown	0 (0)	1 (1)
Lymphocyte immunophenotype, n (%)[a]		
CD5	120 (100)	121 (100)
CD19	120 (100)	119 (98)
CD20	101 (84)	97 (80)
History of splenectomy, n (%)	11 (9)	4 (3)

N (total number of patients in the group) = denominator in calculating percentage;
SD = standard deviation

[a] A patient was counted in all applicable categories.

Table 11 provides a comparison of lymph node findings at baseline based on physical examination and CT/ultrasound. A total of 74% and 75% of patients in the GFC and FC groups, respectively, had abnormal radiographic findings at baseline.

Table 11: Lymph node findings at baseline by method of assessment and treatment group: ITT Population (Study GL303)

Method of assessment		GFC (N = 120)	FC (N = 121)
Physical examination			
Baseline assessment, n (%)		120 (100)	115 (95)[a]
Largest node, n (%)	(0 – < 2 cm)	37 (31)	42 (35)
	(≥ 2 – ≤ 5 cm)	65 (54)	55 (46)
	(> 5 cm)	16 (13)	15 (12)
	Abnormal[b]	2 (2)	3 (2)
Median (range), cm^2		13.5 (0-181)	12.5 (0-387)
CT/ultrasound			
Baseline assessment, n (%)		93 (78)	98 (81)
Largest node, n (%)	(0 – < 2 cm)	12 (10)	16 (13)
	(≥ 2 – ≤ 5 cm)	33 (28)	33 (27)
	(> 5 cm)	39 (33)	36 (30)
	Abnormal[b]	9 (8)	13 (11)
Median (range), cm^2		11 (0 – 438)	8 (0 – 509)

N (total number of patients in the group) = denominator in calculating percentage; "largest node" = node with longest diameter

[a] Lymph node measurements were missing for 6 patients in the FC group. All of these patients had lymphadenopathy based on CT/ultrasound at baseline.

[b] Noted to be abnormal but no measurement recorded

All patients had evidence of active disease. The overall difference between treatment groups in the number of signs/symptoms was significant ($p < 0.035$ [Mantel-Haenszel chi-square test]), with more signs/symptoms recorded in the GFC group than in the FC group (see Table 12).

Table 12: Signs/symptoms at baseline by treatment group: ITT Population (Study GL303)

Sign/symptom	GFC (N = 120) n (%)	FC (N = 121) n (%)
No. of signs/symptoms		
0 – 1	13 (11)	26 (21.5)
2 – 3	83 (69)	77 (64)
≥ 4	24 (20)	18 (15)
Weight loss > 10% prior to enrollment	17 (14)	15 (12)
Fatigue ≥ Grade 2	35 (29)	30 (25)
Fever	7 (6)	4 (3)
Night sweats	43 (36)	38 (31)
Worsening anemia or thrombocytopenia	48 (40)	40 (33)
Hepatomegaly or splenomegaly	59 (49)	58 (48)
Hepatomegaly	24 (20)	24 (20)
Splenomegaly	51 (42.5)	51 (42)
Massive splenomegaly	29 (24)	22 (18)
Lymphadenopathy	111 (93)	109 (90)
Progressive lymphocytosis	62 (52)	55 (46)

N (total number of patients in the group) = denominator in calculating percentage

The treatment groups generally were evenly balanced with respect to types of previous systemic CLL therapy (see Table 13). The Sponsor determined patients' prior response to fludarabine as relapsed or refractory according to criteria used in the pivotal trial of alemtuzumab.(46) Nearly 60% of patients in both groups were insensitive to fludarabine at the time of enrollment. At least 70% of patients in both groups had received prior therapy with cyclophosphamide or chlorambucil, and 28% of patients in each treatment group had been previously treated with rituximab. More than half the patients in both groups had a response to last therapy not more than 6 months in duration.

Table 13: Prior treatment history by treatment group: ITT Population (Study GL303)

	GFC (N = 120)	FC (N = 121)
Prior fludarabine, n (%)		
Relapsed (sensitive)	51 (42.5)	50 (41)
Refractory	69 (58)	71 (59)
Number of prior fludarabine cycles[a]		
Mean (SD)	6.9 (5.84)	5.5 (3.15)
Median	6.0	6.0
Number of prior regimens, n (%)		
1 – 2	60 (50)	63 (52)
≥ 3	60 (50)	58 (48)
Response to last therapy, n (%)		
> 6 months	54 (45)	52 (43)
≤ 6 months	66 (55)	69 (57)

N (total number of patients in the group) = denominator in calculating percentage
[a] If not reported in the case report form, the number of prior cycles of fludarabine was estimated as the number of months treated with fludarabine.

Treatment groups were well balanced at baseline with respect to prognostic factors (see Table 14).

Table 14: Baseline prognostic factors by treatment group: ITT Population (Study GL303)

Factor	GFC N = 120	FC N = 121
Baseline hemoglobin level		
< 11 g/dL, n (%)	32 (27)	39 (32)
≥ 11 g/dL, n (%)	87 (72.5)	82 (68)
Missing	1	0
Mean (SD), g/dL	12.0 (1.99)	11.8 (2.11)
Median, g/dL	12.1	12.0
Baseline platelet count		
< 100,000, n (%)	43 (36)	43 (35.5)
≥ 100,000, n (%)	77 (64)	78 (64.5)
Mean (SD), x $10^3/\mu L$	133.5 (60.23)	138.1 (72.91)
Median, x $10^3/\mu L$	130.0	120.0
Absolute lymphocyte count, x $10^3/\mu L$		
Mean (SD), x $10^3/\mu L$	79.6 (106.68)	77.7 (88.62)
Median, x $10^3/\mu L$	39.5	48.3
Missing	0	1
Cytogenetics, n (%)		
13q− alone	5 (4)	3 (2.5)
Normal	19 (16)	20 (16.5)
13q− and other[a]	13 (11)	6 (5)
Other[a]	14 (12)	17 (14)
Not available	69 (57.5)	75 (62)
Baseline beta-2 microglobulin, n (%)		
< 4 mg/L	57 (47.5)	58 (48)
≥ 4 mg/L	52 (43)	47 (39)
Missing	11 (9)	16 (13)
Baseline LDH level, n (%)		
Non-elevated[b]	63 (52.5)	63 (52)
Elevated	53 (44)	52 (43)
Missing	4 (3)	6 (5)

N (total number of patients in the group) = denominator in calculating percentage
[a] Includes such factors as 17p−, trisomy 12, 11q−, 6q−, and others
[b] Less than the upper limit of normal range

Medical history findings were similar in the 2 treatment groups. Noteworthy differences included (GFC group vs. FC group):

- an increased prior incidence of herpes zoster infection (15% vs. 11%), fatigue (13% vs. 9%), back pain (8% vs. 3%), and thrombocytopenia in the GFC group (14% vs. 7%)
- an increased prior incidence of sinusitis (14% vs. 20%), pneumonia (12% vs. 17%), and drug hypersensitivity (13% vs. 20%) in the FC group

Of the 241 patients in the ITT Population, 11 (5%) patients did not initiate protocol therapy (see Table 15).

Table 15: Disposition of patients not treated by treatment group (Study GL303)

Reason for not initiating protocol therapy	GFC n	FC n
Total	5	6
Withdrawal of consent	2	3
Adverse event	2[a]	1[b]
Violation of the protocol	1	1
Other	0	1[c]

[a] One patient had thrombocytopenia and 1 patient had an opportunistic infection (*Pneumocystis carinii* pneumonia).
[b] The patient had diarrhea, fever, and a urinary tract infection.
[c] The patient did not wish to be treated.

The 230 patients who initiated protocol therapy included 115 patients in each treatment group; in the ITT Population, 36 (30%) patients in the GFC group and 45 (37%) patients in the FC group completed protocol therapy.

Premature discontinuation of protocol therapy prior to completion of 6 cycles was recorded for 84 (70%) patients in the GFC group and 76 (63%) patients in the FC group. In both groups, the primary reason for premature discontinuation of protocol therapy was adverse event/toxicity (GFC group, 43 [36%] patients; FC group, 42 [35%] patients). Disease progression was the next reason most often given for discontinuation of protocol therapy in both treatment groups (GFC group, 20 [17%] patients; FC group, 17 [14%] patients). The median number of cycles of protocol therapy completed was identical in each treatment group (4.0 cycles).

Among the 115 treated patients in the GFC group, 48 (42%) patients each had dose delays with fludarabine and cyclophosphamide. Among the 115 treated patients in the FC group, 39 (34%) patients had dose delays with fludarabine and 40 (35%) patients had dose delays with cyclophosphamide. In both treatment groups, the primary reason for dose delay was adverse event/toxicity. Associated most often with delays or interruptions in administration were thrombocytopenia, fever, and rigors in the GFC group and fever in the FC group.

Among the 115 treated patients in the GFC group, reductions in the dose of fludarabine and cyclophosphamide were recorded for 38 (33%) and 39 (34%) patients, respectively. Among the 115 treated patients in the FC group, dose reductions of fludarabine and cyclophosphamide were recorded for 28 (24%) and 29 (25%) patients, respectively. In both treatment groups, the primary reason for dose reduction was adverse event/toxicity and thrombocytopenia was the adverse event most often associated with dose reduction.

Descriptive statistics for the total (cumulative) dose of Genasense, fludarabine, and cyclophosphamide are provided in Table 16.

Table 16: Descriptive statistics for total (cumulative) dose of study medication across all cycles by treatment group: ITT Population (Study GL303)

	GFC (N = 120)			FC (N = 121)	
	Genasense (mg/kg)	**Flu (mg/m^2)**	**Cy (mg/m^2)**	**Flu (mg/m^2)**	**Cy (mg/m^2)**
n	115	106	106	115	115
Mean (SD)	71.8 (39.11)	258.4 (127.11)	2530.5 (1202.42)	277.5 (132.75)	2767.5 (1321.00)
Median	65.75	244.2	2287.2	262.4	2612.0
25th, 75th percentiles	41.1, 110.3	147.0, 363.0	1470.1, 3587.6	150.6, 428.4	1502.3, 4278.5
Minimum, maximum	2.6, 147.9	49.3, 678.3	498.0, 4763.3	49.1, 469.1	491.1, 4691.1

SD = standard deviation

4.3.3 Efficacy Findings

4.3.3.1 Response Rate (Primary Endpoint)

The primary endpoint was met in the Genasense pivotal trial: based on the blinded external review of response for the Intent-to-Treat Population, the proportion of patients with CR or nPR was significantly greater in the GFC group (20 [17%] patients) than in the FC group (8 [7%] patients; p = 0.025; see Table 17). Notably, this response rate included 11 (9%) patients in the GFC group who had a CR, compared with 3 (2.5%) patients in the FC group (p = 0.03).

Table 17: Number (%) of patients achieving a CR or nPR by treatment group: ITT Population (Study GL303)

	GFC (N = 120)	FC (N = 121)	P value
Patients with CR or nPR, n (%)[a, b]	20 (17)	8 (7)	
Continuity-corrected Pearson Chi-square test			0.025
Fisher's exact test			0.016
Odds ratio (95% confidence interval)		2.83 (1.19-6.70)	
CR, n (%)[a]	11 (9)	3 (2.5)	0.030[c]
nPR, n (%)[a]	9 (7.5)	5 (4)	

N (total number of patients in the group) = denominator in calculating percentage
[a] Response based on the external clinical expert's blinded review
[b] Odds of response in the GFC group compared with the odds of response in the FC group
[c] Fisher's exact test

Baseline characteristics of those patients who achieved a CR/nPR are summarized in Table 18.

Table 18: Baseline characteristics of patients achieving CR/nPR by treatment group: ITT Population (Study GL303)

	GFC (N = 20)	FC (N = 8)
Median (range) age, years	62 (35-76)	69 (52-71)
Median (range) hemoglobin value, g/dL	13 (10.4-15.9)	13 (9.4-14.8)
Median (range) platelet count, x $10^3/\mu L$	160 (42-291)	133 (100-263)
Median (range) lymph node size[a], cm^2		
Based on physical exam	12.3 (0-96)	10.8 (0-38)
Based on radiologic assessment	3.8 (0-58)	0 (0-14)
Disease-related symptoms, n	13	5
Splenomegaly, n	7	3
Prior splenectomy, n	2	0

[a] Reflects the total area

Among the patients with CR/nPR, the median number of cycles of protocol therapy was 5.5 in both treatment groups (range 3 to 6 cycles in both groups). Prior treatment history for those patients who achieved a CR or nPR is summarized in Table 19. None of these patients had received prior treatment with alemtuzumab.

Table 19: Prior treatment history among patients achieving CR/nPR by treatment group: ITT Population (Study GL303)

	GFC (N = 20)	FC (N = 8)
Median (range) number of prior fludarabine cycles	6 (2-10)	3 (1-9)
"Fludarabine sensitive,"[a] n	13	3
Cyclophosphamide/chlorambucil, n	12	5
Rituximab, n	3	0
Other agents, n	10	4

[a] As defined in the literature, response of PR or better lasting for at least 6 months (46)

Patients with CR/nPR were further assessed based on the stratification factors employed in the study (see Section 4.3.1 and Table 20). In each category of patients established by stratification factor, the GFC regimen was superior to FC alone. However, the greatest benefit (almost 4 times greater) was observed in patients who remained sensitive to fludarabine, had received not more than 2 prior regimens, and had a response to last therapy that lasted more than 6 months.

Table 20: CR/nPR by prior systemic therapy and treatment group: ITT Population (Study GL303)

	GFC (N = 120) n/N (%)	FC (N = 121) n/N (%)	P value[a]
Prior fludarabine[b]			
Relapsed (sensitive)	13/51 (25)	3/50 (6)	0.012
Refractory	7/69 (10)	5/71 (7)	NS
Number of prior regimens			
1-2	14/60 (23)	4/63 (6)	0.010
≥ 3	6/60 (10)	4/58 (7)	NS
Response to last therapy			
> 6 months	12/54 (22)	3/52 (6)	0.024
≤ 6 months	8/66 (12)	5/69 (7)	NS

N (total number of patients in the group) = denominator in calculating percentage; NS = not significant

[a] Fisher's exact test

[b] Based on sponsor's assessment according to literature-based criteria and using information recorded on the case report form (46)

Although the limited data do not allow conclusions to be drawn with regard to the impact of cytogenetics on efficacy, response was observed in 2 patients in each group who had "poor" risk cytogenetic factors (17p– or 11q–).

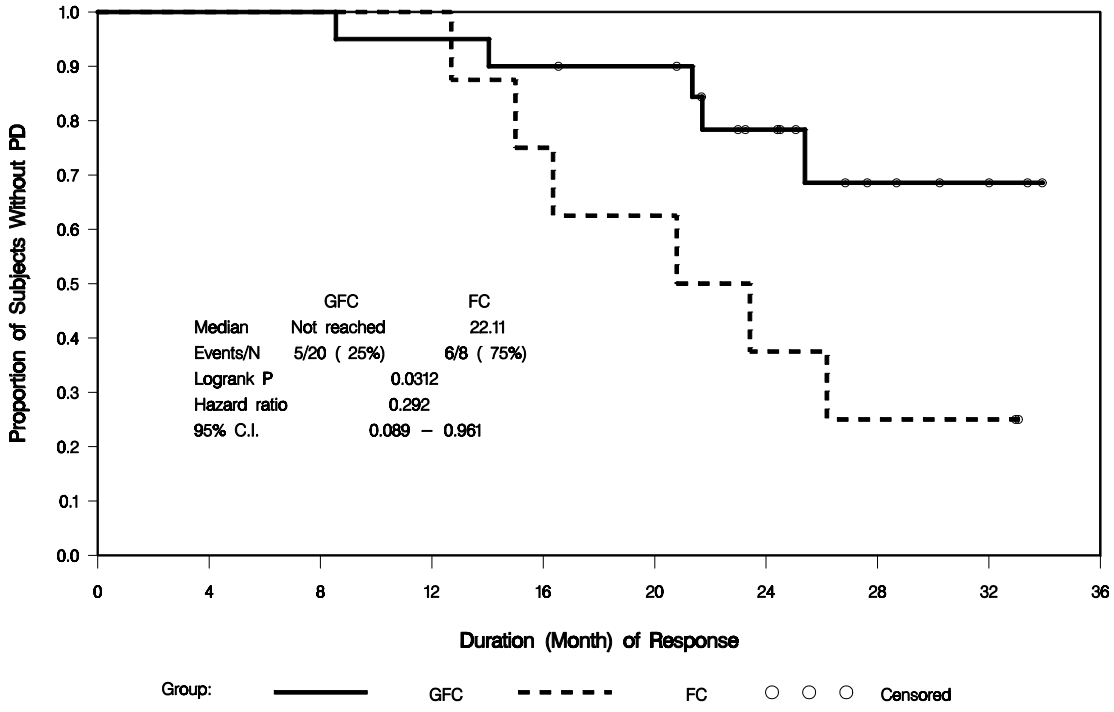
4.3.3.2 Overall Response Rate

Based on the blinded external review of response for the Intent-to-Treat Population, 49 (41%) patients in the GFC group and 54 (45%) patients in the FC group achieved a CR, nPR, or PR at any time (best response; p = 0.64).

4.3.3.3 Duration of Response

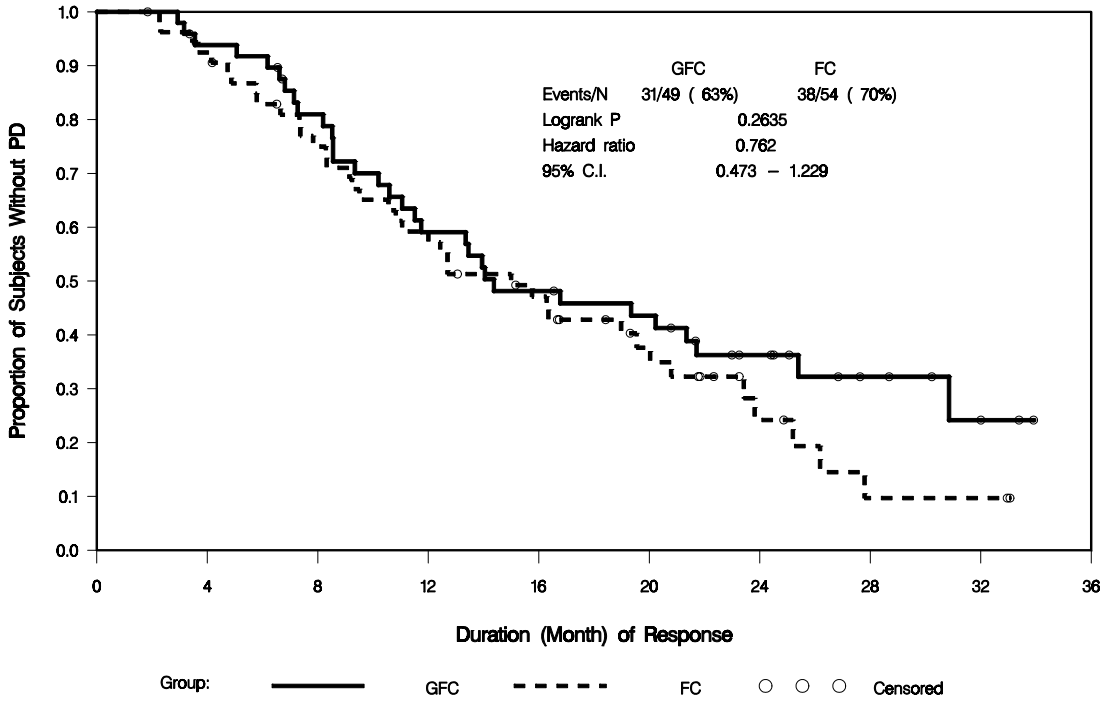
Kaplan-Meier curves for duration of response are shown in Figure 9 by treatment group for those patients who achieved a CR/nPR, as determined by the external clinical expert. Disease progression occurred in 5 of 20 (25%) patients in the GFC group and 6 of 8 (75%) patients in the FC group (p = 0.03).

Figure 9: Duration of response from date of first response among patients achieving CR/nPR by treatment group (Study GL303)



Kaplan-Meier curves for duration of response are shown in Figure 10 by treatment group for those patients who achieved a CR/nPR/PR, as determined by the external clinical expert.

Figure 10: Duration of response from date of first response among patients achieving CR/nPR/PR by treatment group (Study GL303)



Among all responding patients, there was a trend in durability of overall response that favored the GFC group.

Flow cytometry data were available for approximately 75% (21/28) of the patients who achieved a CR/nPR across both treatment arms. There was a trend in favor of the addition of Genasense in terms of the percentage of CR/nPR patients who achieved a flow-cytometric–negative status (GFC group, 69% [11/16 patients]; FC group, 40% [2/5 patients]).

4.3.3.4 Time to Progression

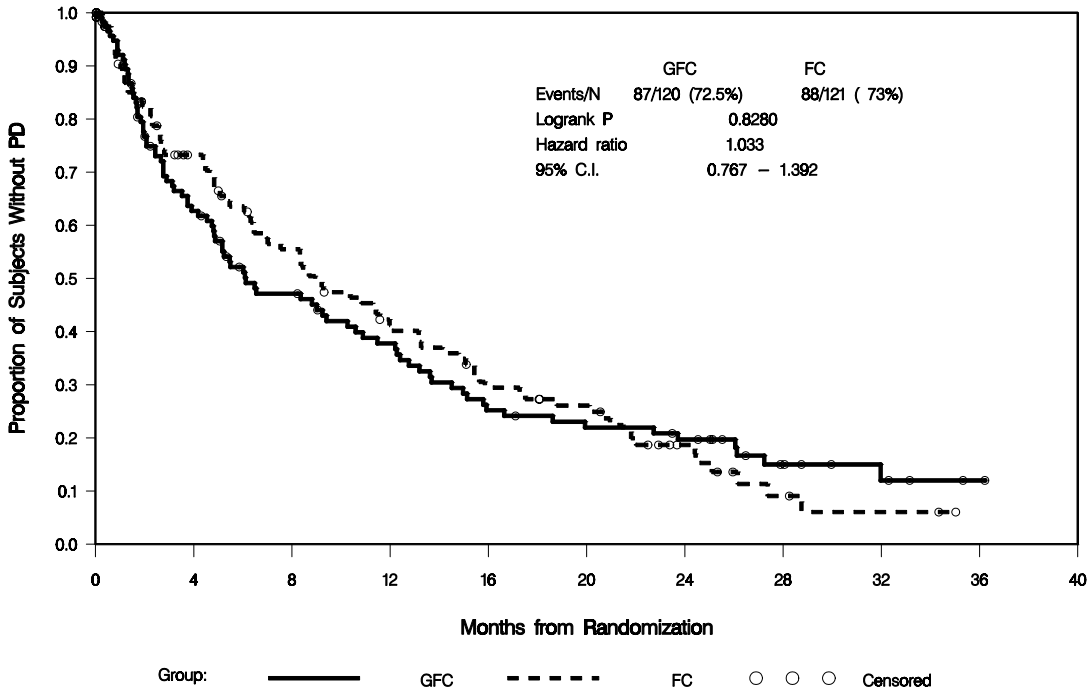
The percentage of patients with disease progression based on the blinded external review after all patients had been followed for a minimum of 24 months from randomization was similar in the 2 groups: 72.5% in the GFC group and 73% in the FC group (see Table 21 and Figure 11).

Table 21: Progression from date of randomization by treatment group: ITT Population (Study GL303)

	GFC (N = 120) n (%)	FC (N = 121) n (%)
Patients with disease progression	87 (72.5)	88 (73)
Patients censored	33 (27.5)	33 (27)
Ongoing without disease progression at the time of last assessment	21 (17.5)	19 (16)
Use of other CLL therapy	7 (6)	7 (6)
Censored at Day 1	5 (4)	7 (6)

N (total number of patients in the group) = denominator in calculating percentage

Figure 11: Kaplan-Meier curves for time to progression by treatment group: ITT Population (Study GL303)



The time-to-progression curves are essentially overlapping with a hazard ratio of 1. At the tails of the curves (approximately 21 months), separation occurs in favor of the addition of Genasense. This separation is driven by patients with durable CR/nPR, who were more numerous in the Genasense arm.

A Cox Model was employed to examine the effect of factors that might potentially influence outcome with regard to time to progression. These factors included age, gender, Rai stage, CD38 expression, beta-2 microglobulin,

hemoglobin, platelet count, and serum LDH at baseline, as well as randomization strata. Adjustment for these covariates resulted in a hazard ratio of 1.00 ($p = 0.98$), yielding a result consistent with the unadjusted time to progression analysis.

4.3.3.5 Clinical Benefit

The achievement of CR is generally recognized as connoting clinical benefit. This association was confirmed by exploratory analyses of symptom-free duration in patients in the ITT Population, as well as in patients with CR/nPR. The following symptoms were included in this analysis: fever, night sweats, fatigue, abdominal discomfort or early satiety due to hepatosplenomegaly, impaired cosmesis due to lymphadenopathy, impaired mobility due to lymphadenopathy, and "other" as reported on the case report form.

In these analyses, the onset of symptom-free status among patients with symptoms was designated as occurring at the midpoint of the interval between the first symptom-free visit and the prior visit. The recurrence of symptoms among patients who were previously symptom free was designated as occurring at the midpoint of the interval between the last symptom-free visit and the subsequent visit. The number of symptom-free days was then calculated. A minimum of 180 days (6 months) of symptom-free status was considered clinically meaningful.

The results of the analysis of symptom-free status in the ITT Population (irrespective of treatment assignment) are presented in Table 22 by response category (ie, patients with CR/nPR and patients with PR).

Table 22: Symptom-free status prior to disease progression or initiation of new therapy among patients who were symptomatic at baseline by response category: ITT Population (Study GL303)

	CR/nPR n (%)[a]	PR n (%)[a]	< PR n (%)[a]	Total
Symptomatic at baseline[b]	18	61	121	200
Symptom-free for ≥ 6 months				
Yes	17 (94)	36 (59)	7 (6)	60 (30)
No	1 (6)[c]	25 (41)	114 (94)	140 (70)

[a] Percentages based on the number of patients who were symptomatic at baseline within the specific response category

[b] Defined as having at least 1 of the following symptoms at baseline: fever, night sweats, fatigue, abdominal discomfort or early satiety due to hepatosplenomegaly, impaired cosmesis due to lymphadenopathy, impaired mobility due to lymphadenopathy, or "other" symptoms as recorded on the case report form

[c] Includes 1 patient in the GFC group for whom fatigue was reported after 5 months without symptoms

Achievement of CR/nPR was associated with the disappearance of all pre-defined symptoms of CLL for a minimum of 6 months in all patients except for one for whom symptomatic benefit lasted 5 months, whereas patients with PR had a 59% chance of achieving this clinical benefit. The Pearson Chi-square p-value for the correlation between response category and durable symptom relief is highly significant ($p < 0.0001$) and supports the association of response with clinical benefit.

Patients who achieved a CR/nPR had approximately 11 more months (323 days) of symptom-free time compared with patients who achieved a PR. Cumulatively, the symptom-free duration for the 20 patients who achieved CR/nPR in the GFC group was 422 months compared to 163 months for the 8 patients who achieved CR/nPR in the FC group.

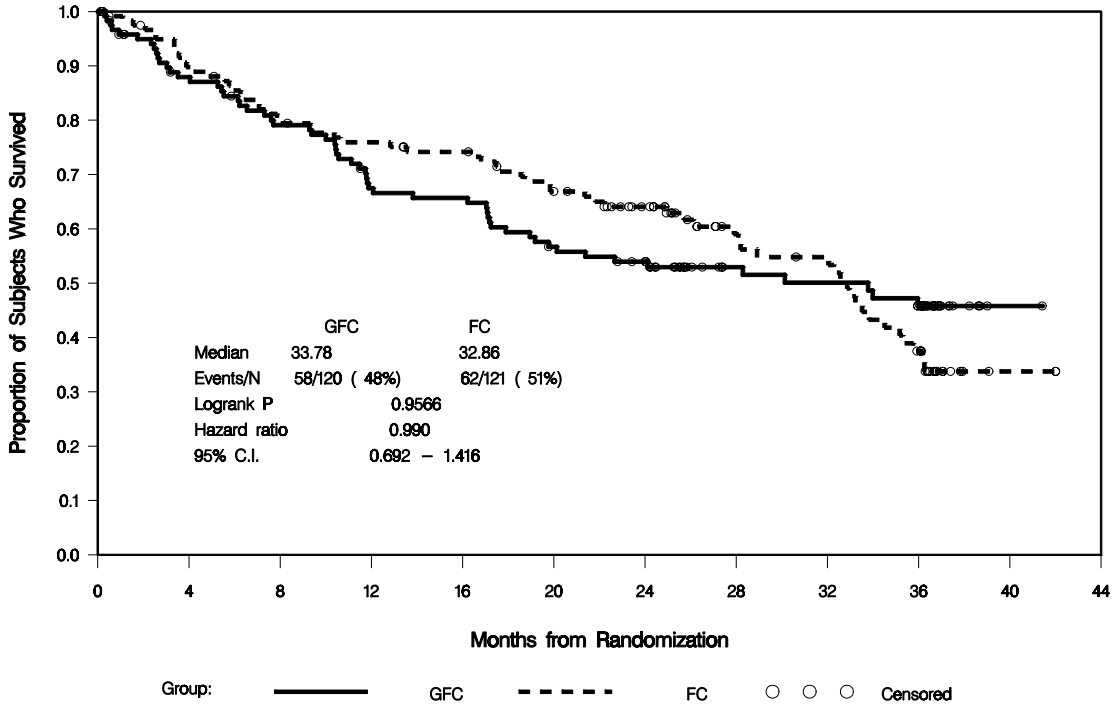
Analyses of other clinical benefit endpoints showed no statistically significant difference in findings between treatment groups. Rather, the clinical benefit associated with the addition of Genasense to the FC regimen is an outcome of the significant increase in durable CR and nPRs as manifested by an increased number of patients with durable symptom-free time.

4.3.3.6 Survival

With follow-up of all patients for 36 months from the date of randomization (as required by protocol), the estimated median survival was 33.8 months in the GFC group and 32.9 months in the FC group (see Figure 12). There is a separation at the tails of the curves in favor of the GFC treatment. The estimated survival rate at 36 months was 46% in the GFC group and 37.5% in the FC group.

These data were not available at the time of the NDA filing and are provided in this briefing document for completeness of information.

Figure 12: Overall survival by treatment group: ITT Population (Study GL303)



4.4 Efficacy Discussion and Conclusion

In the Phase 1-2 study in 40 patients with refractory or relapsed CLL, Genasense monotherapy provided limited but measurable activity, including a PR in 2 heavily pretreated patients and a reduction in hepatosplenomegaly, lymphadenopathy, and/or a lowering of elevated lymphocyte counts in approximately 50% of patients. Tumor lysis syndrome also occurred in 2 patients.

In the randomized Phase 3 study in 241 patients with refractory or relapsed CLL, the primary endpoint was met: the addition of Genasense to FC significantly increased the proportion of patients who achieved a CR or nPR (17% vs. 7%; $p = 0.025$), as determined by the blinded external clinical expert when each patient had been followed for at least 6 months after ending protocol therapy.

Achievement of this endpoint provided clear clinical benefit to these responding patients:

- All CR/nPRs were durable (ie, lasting 6 months or longer from time of initial response). Notably, remission duration was significantly longer in CR/nPR patients who received GFC compared with CR/nPR patients who received FC alone (median not yet reached vs. 22 months, respectively; $p = 0.03$).
- All CRs/nPRs (with 1 exception in the GFC group) were associated with durable relief of disease-related symptoms, including fever, night sweats, fatigue, abdominal discomfort or early satiety due to hepatosplenomegaly,

impaired cosmesis due to lymphadenopathy, impaired mobility due to lymphadenopathy, and "other." Fatigue was reported for the 1 exception in the GFC group who had been symptom-free for 5 months.

- The time-to-progression curves and overall survival curves were similar, supporting that the addition of Genasense to FC had no deleterious effect on patients who achieved less than a CR/nPR. Moveover, the tails of these curves favored the GFC regimen, as driven by the increased number of patients in the GFC group who achieved CR/nPR.

The GFC regimen was superior across all prospectively defined strata. Exploratory analysis suggested that patients who remained chemosensitive, ie, were fludarabine sensitive, had been treated with not more than 2 prior regimens, or had a duration of response to last prior therapy > 6 months in duration derived a greater benefit from the addition of Genasense to FC than other patients.

Conclusion

A 7-day continuous intravenous infusion of Genasense 3 mg/kg/d enhances the efficacy of standard FC chemotherapy in patients with refractory or relapsed CLL.

5. SAFETY IN RELAPSED OR REFRACTORY CLL

The clinical development program for Genasense included 23 studies, of which 18 were completed and 5 were ongoing at the time of the NDA filing. In these studies, Genasense has been administered to a total of 1,170 patients, including 933 patients who received Genasense in completed studies and 237 patients who received Genasense in ongoing studies, as follows:

- 18 completed studies in which a total of 1,518 patients received Genasense only or Genasense in combination with chemotherapy (n = 933) or chemotherapy only (n = 585)
- 5 ongoing studies in which a total of 376 patients received Genasense only or Genasense in combination with chemotherapy (n=237) or chemotherapy only (n = 139)

The 18 completed studies were conducted in patients with various hematologic malignancies (CLL, lymphoma, multiple myeloma) and in patients with various solid tumors (advanced melanoma, breast cancer, prostate cancer, and other cancers) and included randomized studies in CLL, multiple myeloma, and advanced melanoma and 15 nonrandomized studies. The summary of adverse events included in this document is based primarily on the treatment-emergent adverse events (TEAEs) reported in the Phase 3 study in CLL (GL303).

5.1 Phase 1-2 Study: Genasense Monotherapy (GL208)

The adverse event profile of Genasense monotherapy in patients with CLL was clearly defined in the the Phase 1-2 study (GL208). All 40 patients except 1 experienced TEAEs (primarily Grade 1 and Grade 2 in severity; NCI-CTC, Version 2.0), the most common being pyrexia (32.5% of patients); fatigue (30%); cough and hypotension (20% each); and anemia, thrombocytopenia, nausea, and night sweats (17.5% each). The most common laboratory abnormalities were decreases in absolute neutrophil count and platelet count, with 33% and 22.5% of patients experiencing decreases from baseline in these laboratory parameters, respectively, of at least 2 NCI CTC grades. All Grade 3 and Grade 4 events were single occurrences of specific events except for 2 occurrences of Grade 3 thrombocytopenia. Two (7%) patients had a TEAE with an outcome of death (1 patient each with thrombocytopenia and pulmonary embolism); both deaths occurred more than 30 days after the last administration of Genasense, and neither event was considered by the investigator to be related to Genasense.

5.2 Randomized Phase 3 Study: Genasense in Combination with FC (GL303)

In the Genasense pivotal study, 115 patients were treated with GFC and 115 were treated with FC alone. Nearly all patients had at least 1 TEAE regardless of the

treatment administered. These events were primarily Grade 1 and Grade 2 in severity in both groups (NCI-CTC, Version 2.0).

Table 23 provides a summary of frequently reported TEAEs (ie, events [all grades] that were reported in ≥ 15% of patients in either treatment group).

Table 23: Frequently reported TEAEs (ie, events [all grades] reported for ≥ 15% of patients in either treatment group) by preferred term and treatment group: Safety Population (Study GL303)

	All grades		Grade 3		Grade 4	
Preferred term[a,b]	**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
Pyrexia	48	29	3.5	3	0	0
Fatigue	44	31	6	3	0	2
Anaemia NOS	39	42	11	10	3.5	5
Vomiting NOS	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 NOS	23.5	14	1	3	0	0
Diarrhoea NOS	22	14	1	1	0	0
Dyspnoea NOS	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

N (total number of patients in the group) = denominator in calculating percentage

[a] If a patient had multiple occurrences of the same TEAE, the patient was counted in that preferred term based on the occurrence of greatest intensity.

[b] Presented in descending order based on findings in the GFC group

TEAEs reported in at least 30% of patients in both treatment groups included nausea, thrombocytopenia, fatigue, and anemia. Additional adverse events that occurred in at least 30% of patients included fever and vomiting in the GFC group and neutropenia in the FC group.

With the exception of anemia and neutropenia, more patients treated with GFC than FC experienced these frequently reported events, with the most notable difference between treatment groups observed with nausea (GFC group, 72% of patients; FC group, 48%). The incidence of other frequently reported TEAEs was similar (< 10% difference) between the treatment groups except for the events of pyrexia (GFC group, 48%; FC group, 29%); fatigue (GFC group, 44%; FC group, 31%); dehydration (GFC group, 17%; FC group, 2%), weight decreased (GFC group, 16.5%; FC group, 5%), and catheter-related complications (GFC group, 16%; FC group, 3%).

5.2.1 Hematologic TEAEs

Neutropenia and anemia: The addition of Genasense to FC did not result in an increase in the incidence of anemia or neutropenia (all grades) or Grade 3 and Grade 4 abnormalities in absolute neutrophil count or hemoglobin (see Table 23). Rather, the incidence of neutropenia was increased in the FC group and the incidence of anemia was similar in the 2 groups.

Median neutrophil counts and hemoglobin values at the end of Week 1 of each treatment cycle were similar between treatment groups (see Figure 13 and Figure 14, respectively).

Figure 13: Median and interquartile range (25th and 75th percentiles) for neutrophil counts at Week 1 of each cycle by treatment group: Safety Population (Study GL303)

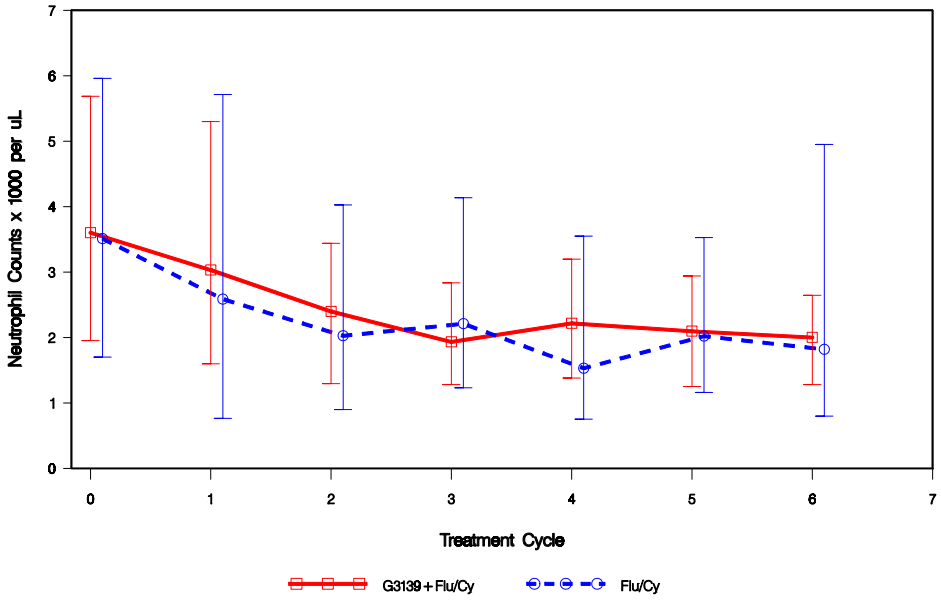
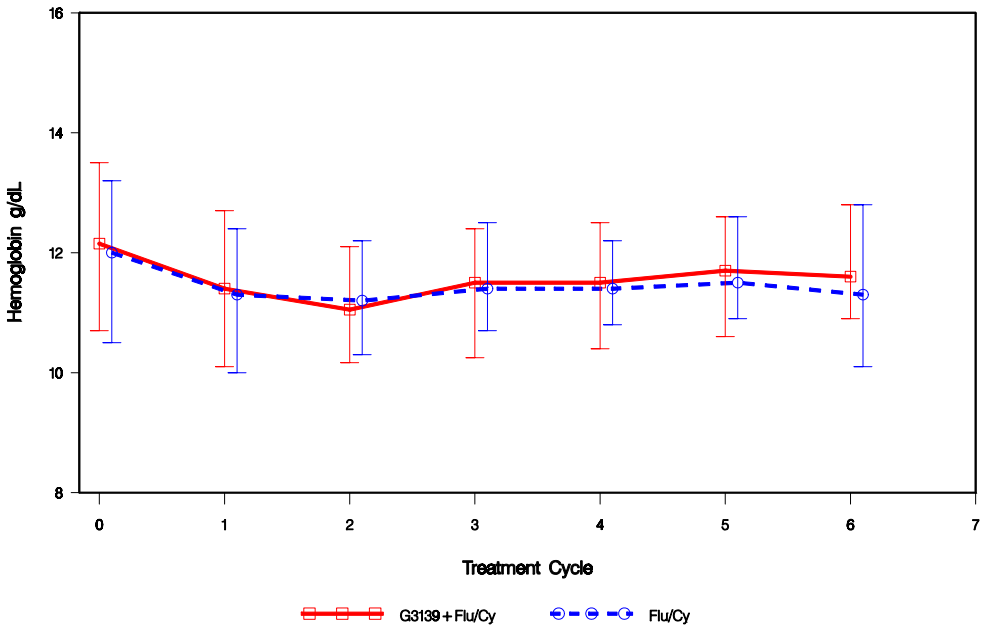
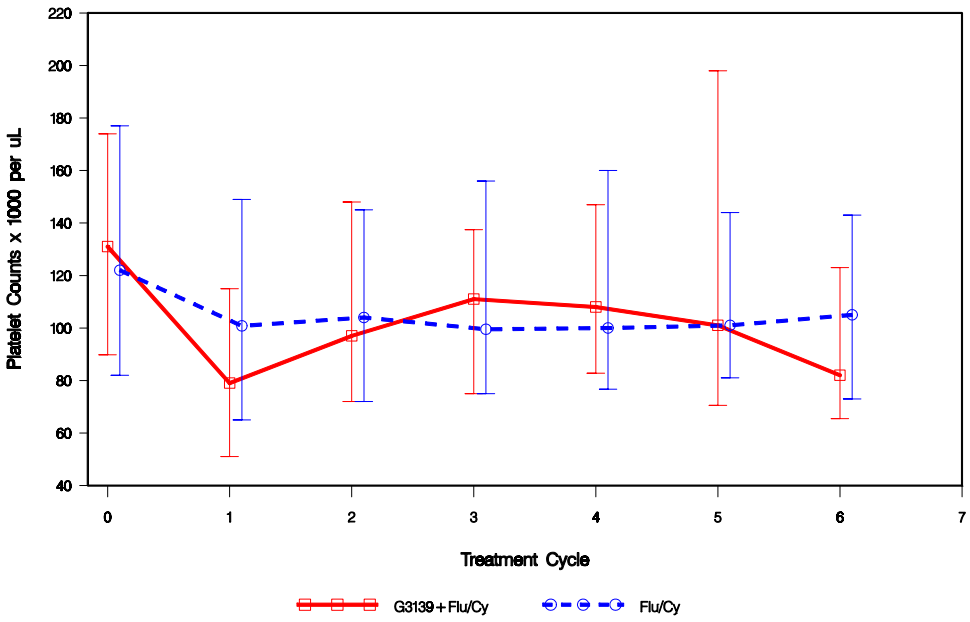


Figure 14: Median and interquartile range (25th and 75th percentiles) for hemoglobin values at Week 1 of each cycle by treatment group: Safety Population (Study GL303)



Thrombocytopenia: An increase in the incidence of thrombocytopenia was observed among patients in the GFC group, including Grade 3 and Grade 4 occurrences (GFC group, 33% of patients; FC group, 20% of patients; see Figure 15). Recovery in platelet counts was apparent by Cycle 2.

Figure 15: Median and interquartile range (25th and 75th percentiles) for platelet counts at Week 1 of each cycle by treatment group: Safety Population (Study GL303)



Platelet transfusions were administered to 21 (18%) patients in the GFC group and 6 (5%) patients in the FC group during treatment (including the 30-day period following the last dose of study medication), with the majority of these patients receiving platelet transfusions in Cycle 1 (GFC group, 13 of 21 patients; FC group, 6 of 6 patients). In most patients, platelet transfusions were administered when platelet counts were > 10,000 but < 25,000 and were not associated with a bleeding event (see Table 24). Decreases in platelets associated with transfusions most often occurred in patients with baseline thrombocytopenia (ie, platelet count < 100,000). Among these patients, more patients in the GFC group than in the FC group received platelet transfusions (GFC group, 29% [12 of 41 patients]; FC group, 10% [4 of 39 patients]).

Table 24: Platelet count at baseline and at time of first transfusion by treatment group: Safety Population (Study GL303)

	< 100,000 at baseline		≥ 100,000 at baseline	
At time of first transfusion	**GFC n = 41**	**FC n = 39**	**GFC n = 74**	**FC n = 76**
No. of patients with platelet count at time of first transfusion[a]	9	2	6	2
≤ 10,000	2	1[b]	1	0
> 10,000 – < 25,000	7[c]	1	5[d]	2[e]

[a] The lower of either the last platelet count prior to transfusion or the first platelet count after transfusion
[b] This patient had rectal bleeding (Grade 1).
[c] One patient had hematuria (Grade 2).
[d] One patient had a subepidermal hemorrhage (Grade 3).
[e] One patient had a hemorrhagic disorder (Grade 3).

Bleeding is the most important clinical complication of significant thrombocytopenia. Notably, although there was a greater incidence of all grades of bleeding events in the GFC group (19% of patients) than in the FC group (8% of patients), the incidence of Grade 3 and Grade 4 bleeding events was low in both treatment groups: 4 (3.5%) and 2 (2%) patients in each group, respectively. The percentage of patients who received RBC transfusions was similar in the 2 treatment groups.

One patient in each group had a Grade 4 bleeding event. Both events occurred in a setting of severe thrombocytopenia. In the GFC group, the patient had a gastric hemorrhage in Cycle 6 and recovered; the platelet count at the end of Cycle 5 had been 122 x 10^3/μL. In the FC group, 1 patient had a cerebrovascular accident on Day 22 of Cycle 1 therapy with FC, which resulted in death; the platelet count prior to initiation of protocol therapy had been 34 x 10^3/μL.

5.2.2 Nonhematologic TEAEs

Catheter-related Events

Catheter-related complications (preferred term; all ≤ Grade 2) were reported for 18 patients treated with GFC and 3 patients treated with FC. The complications included events reported (verbatim terms) as pain, tenderness, soreness, bruising, skin tear, redness, swelling, oozing, bleeding, infiltration at the catheter site, and a reaction to an antiemetic administered intravenously.

Catheter-related infections (all ≤ Grade 3) were reported for 11 patients treated with GFC and 1 patient treated with FC. These infections resolved with no residual effects.

Catheter-related thrombotic events (all ≤ Grade 3) were reported for 2 patients in the GFC group and included subclavian vein thrombosis and jugular vein thrombosis. Both events were related to the indwelling central catheter.

Opportunistic Infections

Opportunistic infections were reported for 5 patients in the GFC group and 8 of patients in the FC group. In the GFC group, these included pulmonary aspergillosis, pulmonary histoplasmosis, progressive multifocal leukoencephalopathy, viral septicemia, and reactivation of hepatitis B. In the FC group, these included herpes simplex (2 patients), herpetic lip lesion (2 patients), *Mycobacterium avium-intracellulare*, varicella zoster, *Candida* sepsis, and viral hepatitis (1 patient each).

First-cycle Infusion-related Reactions

Tumor-lysis syndrome was reported for 2 patients treated with GFC, and a single fatal event of an infusion-related reaction occurred. These events occurred in Cycle 1 and were similar qualitatively to those increasingly reported with current CLL chemotherapies, such as monoclonal antibodies.

Overdoses of Genasense

An accidental overdose of Genasense occurred in 1 patient. This patient was hospitalized after receiving the planned 7-day Cycle 4 infusion of Genasense (1657 mg; 21.1 mg/kg) in 16 hours due to an error in pump programming; FC had not yet been administered. The patient experienced hunger, headaches, rigors, heart palpitations, and fatigue and was hospitalized. Hematologic findings included a white blood cell count of 2.1 x 10^3/μL (baseline 22.9 x 10^3/μL), a neutrophil count of 1.6 x 10^3/μL (baseline 2.06 x 10^3/μL), a hemoglobin of 11.1 g/dL (baseline 13.9 g/dL), and a platelet count of 86 x 10^3/μL (baseline 142 x 10^3/μL). Additional laboratory values included a serum creatinine of 0.9 mg/dL and a BUN of 12 mg/dL. Liver function tests were within normal limits, except for bilirubin, which was slightly elevated at 1.28 mg/dL (baseline 0.47 mg/dL). The patient was treated with 1 liter of intravenous fluid over a 12-hour period. Two days after the overdose occurred, the patient was considered to be recovered and was discharged from the hospital. Therapy with Genasense (an additional 1657 mg) was resumed 5 days later and administration for 7 days was uneventful.

Other safety findings

The incidence of Grade 3 or Grade 4 shifts in serum chemistry parameters postbaseline was low in both treatment groups. Findings between treatment groups were, for the most part, similar; a slightly increased incidence of shifts was observed in the GFC group for increased ALT (5 [5%] patients), increased creatinine (5 [5%] patients), increased glucose (6 [6%] patients), and decreased potassium and decreased sodium (4 [4%] patients each).

5.2.3 TEAEs with an Outcome of Death

A total of 9 (8%) patients in the GFC group and 5 (4%) patients in the FC group had a TEAE with an outcome of death (see Table 25). Treatment groups were similar with respect to the causes of death except for 2 deaths in the GFC group that were due to tumor lysis or an infusion-related reaction.

Among the 9 patients in the GFC group, 5 (4%) patients had an event with an outcome of death that was considered related to treatment (1 patient each with increased blood creatinine, infusion-related reaction, and tumor lysis syndrome and 2 patients with septic shock).

Among the 5 patients with an outcome of death in the FC group, 2 (2%) patients had an event that was considered related to treatment (1 patient each with neutropenic sepsis and pseudomonal pneumonia).

Table 25: TEAEs with an outcome of death by treatment group: Safety Population (Study GL303)

Event[a]	GFC (N = 115) n (%)	FC (N = 115) n (%)
At least 1 TEAE with an outcome of death at any time	9 (8)	5 (4)
Disease progression	2 (2)	1 (1)
Infection		
Septic shock	2 (2)	0
Neutropenic sepsis	0	1 (1)
Pneumonia	0	1 (1)
Pneumonia pseudomonal	0	1 (1)
First-cycle infusion-related events		
Infusion-related reaction	1 (1)	0
Tumor lysis syndrome	1 (1)	0
Organ failure		
Multi-organ failure	0	1 (1)
Renal failure	1 (1)	0
Blood creatinine increased	1 (1)	0
Pulmonary embolism	1 (1)	0

N (total number of patients in the group) = denominator in calculating percentage
A shaded cell represents an event considered related to treatment.
[a] Presented in descending order based on findings in the GFC group

5.2.4 Discontinuations due to TEAEs

In both treatment groups, the percentage of patients who discontinued due to a TEAE was identical (40 [35%] patients) and thrombocytopenia was the most frequently reported event that resulted in discontinuation (GFC group, 10% of patients; FC group, 16% of patients; see Table 26).

Table 26: TEAEs with action taken of discontinued in ≥ 2% of patients in either treatment group by preferred term and treatment group: Safety Population (Study GL303)

Preferred term[a]	GFC (N = 115) n (%)	FC (N = 115) n (%)
Had at least 1 TEAE with action taken discontinued	40 (35)	40 (35)
Thrombocytopenia	11 (10)	18 (16)
Anemia	3 (3)	2 (2)
Neutropenia	3 (3)	7 (6)
Blood creatinine increased	2 (2)	0
Disease progression	2 (2)	1 (1)
Hepatic failure	2 (2)	0
Nausea	2 (2)	0
Platelet count decreased	2 (2)	0
Renal failure	2 (2)	1 (1)
Septic shock	2 (2)	0
Tumour lysis syndrome	2 (2)	0
Febrile neutropenia	1 (1)	3 (3)
Pyrexia	1 (1)	2 (2)
Hemolytic anemia	0	2 (2)

N (total number of patients in the group) = denominator in calculating percentage

[a] Presented in descending order based on findings in the GFC group

5.3 Other Completed Studies and Ongoing Studies

The remaining 17 completed studies (including a randomized study in multiple myeloma and a randomized study in advanced melanoma) were conducted in patients with various hematologic malignancies and solid tumors. In these studies, the type and severity of adverse events among patients receiving combination

therapy was determined by the specific chemotherapy agents administered. No unexpected or new toxicity was identified.

No unexpected or new adverse events have been identified in the 5 ongoing studies.

5.4 Safety Discussion and Conclusion

Consistent with combination regimens in general, the addition of Genasense to standard chemotherapy increased the incidence of some TEAEs. The percentage of patients who discontinued protocol therapy due to a TEAE did not increase in the GFC group (this discontinuation rate was identical in both groups) and the incidence of treatment-related TEAEs with an outcome of death was low in both treatment groups (GFC group, 4% of patients; FC group, 2% of patients).

- Among the hematologic events reported, the incidence of anemia and neutropenia remained unchanged by the addition of Genasense to FC. The incidence of these 2 events was lower in the GFC group than in the FC alone group, and the difference between groups in neutropenia was noteworthy (GFC, 24% of patients; FC, 33%).

  The incidence of thrombocytopenia was increased in the GFC group. Although there was a greater incidence of all grades of bleeding events in the GFC group (19% of patients) than in the FC group (8%), the incidence of Grade 3 and Grade 4 bleeding events was low in both treatment groups (GFC group, 3.5% of patients; FC group, 2%). Only 1 patient in each group had a Grade 4 bleeding event.

  More patients in the GFC group received platelet transfusions (18% of patients) than in the FC group (5%) during treatment. Regardless of treatment group, most of these patients received platelet transfusions in Cycle 1. Consistent with this finding was the observation that decreases in platelet counts associated with transfusions most often occurred in patients with a platelet count < 100,000 at baseline.

  Despite an increase in the incidence of Grade 3 or Grade 4 changes from baseline in platelet counts in the GFC group in Cycle 1, recovery to baseline level was apparent by Cycle 2.

- A very small number of patients in the GFC group had infusion-related events (all in Cycle 1). These events were similar to those increasingly reported with other CLL treatments and were characterized by fever, nausea, dehydration, back pain, renal insufficiency, hypotension, and/or thrombocytopenia and was reversible in most patients with intensive supportive care in the Genasense trial.
- The incidence of catheter-related complications was increased in patients treated with GFC, as was expected given the requirement for a venous access

(usually a central line) for administration of the 7-day continuous intravenous infusion required for Genasense therapy. Overall, the incidence of complications related to central venous catheters was within expected limits and did not impede patients from receiving protocol therapy.

Conclusion

A 7-day continuous intravenous infusion of Genasense 3 mg/kg/d can safely be added to full-dose FC chemotherapy in the outpatient setting under the supervision of a physician experienced in the use of antineoplastic agents. The adverse events associated with GFC were consistent with those commonly observed in the oncology setting. These can largely be prevented and successfully managed when they occur.

6. DISCUSSION AND CONCLUSIONS

The role of Bcl-2 in the pathogenesis of CLL, in particular, and the survival of cancer cells, in general, has been well documented. Genasense, a Bcl-2 antisense agent, relieves Bcl-2–induced apoptosis and thus may improve the effectiveness of coadministered anticancer therapy.

CLL is the most common form of leukemia in adults in Western countries; more than 10,000 new cases are reported in the United States alone each year. Patients in the advanced stages of CLL face a relentlessly progressive clinical course characterized by fever, weight loss, generalized adenopathy, hepatosplenomegaly, and pancytopenia. Treatment in the setting of relapsed disease is associated with increasingly brief response and short survival due to the complications of this illness (usually infection or hemorrhage). The disease is generally regarded as incurable.

Currently approved treatment options for patients with relapsed or refractory CLL are limited to alemtuzumab and fludarabine. The latter drug has been administered in combination with cyclophosphamide in recent years with enhanced efficacy demonstrated, and the FC combination regimen — with or without rituximab, which has not yet been approved for this indication — has emerged as a standard of care in the setting of relapsed or refractory CLL.

Both the alemtuzumab and fludarabine/cyclophosphamide treatment options have recognized limitations with respect to both efficacy and safety.

- Alemtuzumab received accelerated approval in 2001 based on a 2% CR rate and a 31% PR rate in a fludarabine-refractory population. Although a post-hoc, responders-only analysis showed that PRs induced by alemtuzumab were associated with clinical benefit, no minimum duration of symptomatic relief was required. In the pivotal trial, 10% of patients died during treatment or within 30 days of the end of therapy.

  The role of alemtuzumab in the relapsed/refractory setting has not yet been clarified. There is current interest in using alemtuzumab in patients with minimal residual disease after “debulking” with standard cytotoxic drugs such as FC.(11,12,13)

- Fludarabine received approval on the basis of a CR/PR rate of 42% in an alkylating-agent–refractory population using response criteria in place prior to the NCI-WG guidelines.(44) In the 2 pivotal, single-arm trials, responses were not durable, and symptomatic benefit was not reported. More recently, the CR rate with fludarabine alone in previously untreated patients has ranged from 6% to 7%.(20,21) In recent years, this agent has been administered in combination with cyclophosphamide to refractory patients with improved efficacy. However, in the Genasense multicenter, community-based study

with independent assessment of response, the combination of FC had a CR/nPR rate of only 7%. The side-effect profile of the FC regimen is of clinical concern due to the occurrence of such events as second malignancies, immunosuppression, neutropenia, and hemorrhagic disorders.

This NDA for accelerated approval of Genasense in combination with FC supports both the efficacy and safety of this treatment in patients with relapsed or refractory CLL. Achievement of the primary endpoint (ie, a statistically significant improvement in the CR/nPR rate) was accompanied by durability of response (ie, lasting for at least 6 months) in all patients with CR/nPR, and symptomatic relief (ie, absence of CLL symptoms) for at least 6 months was documented in all but 1 patient. Notably, the duration of symptom-free time among patients with CR/nPR across both treatment groups was significantly superior when compared to the duration of symptom-free time among patients achieving PR.

As expected with combination regimens in general, the addition of Genasense to standard chemotherapy increased the incidence of some TEAEs. The identical percentage of patients who discontinued protocol therapy due to a TEAE in the GFC and FC groups suggests that adverse events were tolerable and reversible.

Adverse events with an outcome of death were infrequent among patients treated with the GFC regimen in the Genasense pivotal trial. Of particular note were 3 infusion reactions in Cycle 1, including 2 cases of tumor lysis syndrome and 1 infusion-related reaction, with fatal outcome in 2 cases. These cases support the need for close patient supervision by a physician experienced in the use of antineoplastic agents, with particular attention in Cycle 1 to maintaining adequate hydration and carefully monitoring hematologic changes (the latter of particular importance in patients with a markedly elevated WBC count at baseline).

Overall, in the care of an appropriately qualified physician, adverse events associated with GFC can largely be prevented with prophylactic treatment and are manageable when they occur. Genasense can be administered without a reduction in the dose of FC, and treatment can be provided on an outpatient basis.

Conclusion

Genasense (3 mg/kg/d for 7 days by continuous intravenous infusion) and fludarabine (25 mg/m^2/d intravenously) followed by cyclophosphamide (250 mg/m^2/d intravenously) on Days 5, 6, and 7 of the Genasense infusion is an efficacious and safe therapy for patients with relapsed or refractory CLL.

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Advisory Committee Briefing Document

NDA 21-874

Appendix

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

1. NATIONAL CANCER INSTITUTE-SPONSORED WORKING GROUP GUIDELINES

Site	CR[a,b]	PR[c]	Progressive disease
Lymph nodes	None	≥ 50% decrease from baseline	≥ 50% increase in the sum of the products of at least 2 nodes, 1at least 2 cm; appearance of new nodes on 2 consecutive determinations ≥ 2 weeks apart
Liver/spleen	Not palpable	≥ 50% decrease from baseline	≥ 50% increase below costal margin or appearance of new hepatomegaly or splenomegaly
Constitutional symptoms[d]	None	Not applicable	Not applicable
Polymorphonuclear leukocytes	≥ 1500/μL	≥ 1500/μL or ≥ improvement over baseline	Not applicable
Platelet count	≥ 100,000/mm^3	≥ 50% improvement from baseline or ≥ 100,000/mm^3	Not applicable
Hemoglobin (untransfused)	≥ 11.0 g/dL	≥ 50% improvement from baseline or > 11.0 g/dL	Not applicable
Lymphocytes	≤ 5000/mm^3	≥ 50% decrease from baseline	≥ 50% increase to at least 5000/mm^3
Lymphocyte morphology	Not applicable	Not applicable	Transformation to a more aggressive histology, ie, Richter's syndrome or prolymphocytic leukemia.
Bone marrow aspirate or biopsy	≤ 30% lymphocytes and no lymphoid nodules	Not applicable	Not applicable

[a] Patients who had a complete response by all criteria except persistent lymphoid nodules in bone marrow were classified as nodular partial response. Lymph nodes assessed by CT scan and remaining in areas of previous known disease were considered uninvolved if they measured ≤ 1.5 x 1.5 cm. Lymph nodes of larger size must have been documented to be free of tumor on biopsy, or the same nodes must not have enlarged over a 3-month period following cessation of therapy for a patient to be considered to have a complete response.

[b] Patients with complete response were required to exhibit these criteria for at least 2 months.

[c] Patients who fulfilled the criteria of a complete response, with the exception of a persistent cytopenia that was believed to be treatment related, were considered to have a partial response. Only 1 of the hematologic response criteria must have been met to qualify as partial response if all other criteria were met. Patients with partial response were required to exhibit these criteria for at least 2 months.

[d] Night sweats and fever in Study GL303

2. STATISTICAL METHODS IN STUDY GL303

The following efficacy endpoints were analyzed as described:

Response Rate: The proportion of patients identified by the blinded external clinical expert as having CR or nPR was compared between the treatment groups (ITT Population [ie, all patients randomized]) using a two-sided continuity-corrected Pearson Chi-Square test; the 95% confidence interval for response rate was calculated. Because the continuity-corrected Pearson Chi-square test is overly conservative in estimating a discrete variable as a continuous variable, Fisher's exact test was also used to compare the 2 treatment groups with respect to the proportion of patients with CR/nPR. The 95% confidence interval for response rate was calculated based on a normal distribution.

To adjust for baseline disease characteristics, the proportions were further compared by using the Cochran-Mantel-Haenszel test stratified by randomization stratum. To explore prognostic factors, a logistic regression model was performed employing a stepwise procedure and including treatment and the following variables: (1) randomization stratum, (2) age group (<65 years or ≥ 65 years), (3) gender, (4) Rai Stage (I or II-IV), (5) baseline hemoglobin (< 11 g/dL or ≥ 11 g/dL), (6) baseline platelet count (<100,000/mm³ or ≥ 100,000/mm³), (7) CD38 expression (absent or present), (8) genetic abnormalities (13 q alone, normal, 13q and other, other); (9) beta-2 microglobulin (< 4 or ≥ 4), (10) baseline LDH status (elevated or nonelevated)

Duration of Response: Duration of response (CR, nPR, PR) was calculated from the date when clinical response criteria were first met to the earliest date when either progressive disease was documented as determined by blinded review or other CLL therapy was initiated and was censored at the date of last evaluation of response in the absence of progressive disease or use of other CLL therapy. Among patients with CR/nPR, duration of response was compared between the 2 treatment groups by using the nonstratified log-rank test and presented by Kaplan-Meier curves.

Time to Progression: Time to progression was calculated from the date of randomization to the date of progressive disease determined by blinded review prior to the use of other CLL therapy. For patients who did not have progressive disease prior to use of other CLL therapy, time to progression was censored at the earliest of the start date of other CLL therapy, the time of last response evaluation, or the end of the 3-year period from the date of randomization. Time to progression was analyzed using the non-stratified log-rank test (primary analysis). An additional analysis was performed using the Cox Proportional Hazards Model by employing a stepwise procedure with treatment and the same variables that were included in the logistic regression model of the primary efficacy endpoint. The non-stratified log-rank test was employed as the primary analytical method.

The hazard ratio and 95% confidence interval were estimated using an unadjusted Cox Proportional Hazards Model.

Clinical Benefit: Clinical benefit endpoints were analyzed using the best response achieved during the study and included resolution of B symptoms (night sweats and fever); resolution or reduction of massive splenomegaly; improvement in ECOG Performance Status, disease-related anemia, and fatigue; decreased use of RBC transfusions and dose of erythropoietin; resolution of other disease-related symptoms (ie, early satiety and abdominal discomfort due to hepatosplenomegaly and impaired cosmesis and impaired mobility due to lymphadenopathy). Clinical benefit parameters were analyzed based on best response using descriptive statistics and/or a chi square test, as appropriate.

Overall Response Rate: Overall response (CR + nPR + PR) was assessed using the same method as described for response rate.

Survival: Survival time was calculated from the date of randomization to the date of death and censored at the end of the 3-year period from the date of randomization or at the time a patient was last known to be alive. Survival time was summarized using the same methods as described for time to progression.