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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21, 877

Drug Name: Nelarabine

Indication(s): T-ALL and T-LBL with at least two prior chemotherapy regimens

Applicant: GlaxoSmithKline

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Since the studies submitted to support this application were open label, uncontrolled, and non-randomized no valid statistical comparisons could be made. Clinical judgment is needed to assess the efficacy of this drug.

1.2 Brief Overview of Clinical Studies

The proposed indication for nelarabine is in the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

The sponsor believes that the primary support for the proposed indication comes from the following clinical trials:

COG P9673 (Study PGAA2001): A Phase II Study of 506U78 in Patients with Refractory T-Cell Malignancies.

CALGB19801 (Study PGAA2002): A Phase II Study of Nelarabine (506U78) in Patients with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL).

The study design of the PGAA2001/COGP9673 Phase II trial provided for determination of the efficacy and safety of nelarabine in subjects with relapsed or refractory T-ALL or T-LBL who were ≤ 21 years of age at initial diagnosis, and who received nelarabine administered daily for 5 days, repeated every 21 days. The trial began with a starting dose of 1200 mg/m² but the dose was reduced first to 900 mg/m² and then to 650 mg/m² because of neurotoxicity.

PGAA2002/CALGB19801 was an open-label, multicenter phase II study in adult subjects with refractory or relapsed T-lineage ALL or LBL. Nelarabine was administered by intravenous (IV) infusion at a dose of 1500 mg/m² over 2 hours on days 1, 3, and 5 of a 21 day treatment cycle. The main entry criteria included adults (≥ 16 years) who were refractory to at least one induction treatment regimen or in first or later relapse after achieving a complete response. The study was opened at a dose of 2200 mg/m²/day but was amended to a dose of 1500 mg/m²/day to decrease the risk of neurologic toxicity. Three subjects received the 2200 mg/m² dose.

There were also three Phase I trials (Study PGAA1001; Study PGAA1002; Study PGAA1003) which enrolled a total of 181 subjects, 50 of whom had relapsed or refractory T-ALL/T-LBL. However, only the two phase II studies are reviewed here.

1.3 Statistical Issues and Findings

The two phase II studies submitted to support this application were open label, uncontrolled, and non-randomized so no valid statistical comparisons could be made. The sponsor is seeking an indication for T-ALL and T-LBL patients with at least two prior inductions. In the COG (pediatric and adolescent) study the originally planned dose was 1200 mg/m² but this was reduced first to 900 mg/m² and then to 600 mg/m² because of neurotoxicity. The majority of patients were dosed at 650 mg/m² and this is the dose sought in the indication. Complete responses were observed in 5 of 39 (13% [4%, 27%]) patients in the 2 or more prior inductions subgroup who were treated with the 650 dose. An additional 4 patients in this group achieved CR*s (CR w/out hematologic recovery). So a total of 9 of the 39 (23% [11%, 39%]) patients achieved a CR* or better. In the adult study the dose was 1500 mg/m². In this study, 5 out of 28 (18% [6%, 37%]) achieved a CR and 1 achieved a CR* for a total of 6 out of 28 (21% [8%, 41%]) with a CR* or CR. Clinical judgment is needed to make a recommendation on efficacy since there were no control groups to compare these rates to.

In many cases patients received bone marrow transplants or other systemic or intrathecal therapies after nelarabine treatment and before disease progression. In such cases the observed durations of complete response may be overestimates of the duration of response due to Nelarabine alone.

2 INTRODUCTION

2.1 Overview

Nelarabine (506U78, GI262250), a prodrug of 9-β-D-arabinofuranosylguanine (ara-G), is a deoxyguanosine analogue developed for the treatment of hematologic malignancies. The rationale for development of an analogue of deoxyguanosine is based on the observation that T-cell lymphopenia has been associated with a deficiency in purine nucleoside phosphorylase (PNP).

Two INDs are associated with this drug. One is held by the National Cancer Institute. The other, IND 42,778, is held by the sponsor of this NDA, GlaxoSmithKline. GSK collaborated with the NCI throughout the development of this product.

The proposed indication for nelarabine is in the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

The primary support for the proposed indication comes from the following clinical trials:

COG P9673 (Study PGAA2001): A Phase II Study of 506U78 in Patients with Refractory T-Cell Malignancies.

CALGB19801 (Study PGAA2002): A Phase II Study of Nelarabine (506U78) in Patients with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL).

As no established standards exist for the treatment of patients with relapsed or refractory T-ALL or T-LBL, these studies were conducted as open-label, uncontrolled Phase II studies. PGAA2001 was conducted in children (age \leq 21) and PGAA2002 was conducted in adults.

2.2 Data Sources

The data can be found at the following location:

\\cdsesub1\n21877\n_000\2005-04-29\crt\datasets\

The datasets for the key pediatric study, COGP9673, are located in the following directory.

\\cdsesub1\n21877\n_000\2005-04-29\crt\datasets\pgaa2001\

The EFFICACY.xpt dataset contains the sponsor's derived responder status for each patient.

The LAB.xpt dataset contains the lab data needed to ascertain the responder status.

The datasets for the key adult study, CALGB19801, are located in the following directory.

\\cdsesub1\n21877\n_000\2005-04-29\crt\datasets\pgaa2002\

The EFFICACY.xpt dataset contains the sponsor's derived responder status for each patient.

The LAB.xpt dataset contains the lab data needed to ascertain the responder status.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study PGAA2001/COGP9673

This study was initiated on June 2, 1997 and completed on July 19, 2002.

3.1.1.1 Study Design

This was a phase II, two-stage, open label study of nelarabine in subjects with relapsed or refractory T-ALL or T-NHL who were \leq 21 years of age at initial diagnosis. Nelarabine was to be administered daily for 5 days, repeated every 21 days. The trial began using the starting dose of 1200 mg/m² but was decreased first to 900 mg/m² and then to 650 mg/m² because neurotoxicity was observed. Subjects were entered into one of the following four strata as appropriate.

- Stratum 01: T-ALL or T-NHL in first relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse – other than CNS).
- Stratum 02: T-ALL or T-NHL in second or later relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse – other than CNS).
- Stratum 03: T-ALL or T-NHL with positive bone marrow and CSF (>5% bone marrow blasts and CNS 2 or 3 involvement); CNS 2: subjects with <5 WBC/mm³ and positive cytology; CNS 3: subjects with ≥5 WBC/mm³ and positive cytology.
- Stratum 04: Extramedullary relapse and <25% bone marrow blasts in the bone marrow (excluding isolated CNS relapse).

3.1.1.2 Efficacy and Safety Assessments

Table 1 shows the assessment schedule for the study. Bone marrow assessments (BMA) were to take place at day 21 of cycle 1 (week 3) and day 21 of cycle 2 (week 6). If week 6 was the first time a CR was documented then another BMA was to be done at week 9 to confirm the CR.

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Table 1 PGAA 2001: Scheduled Assessments

STUDIES TO BE DONE	PRE-STUDY	ON STUDY	OFF STUDY
Complete history	X		
Serum pregnancy tests (females only)	X		
Physical exam with attention to neurologic exam, interval history, performance, symptoms (w/TPR, BP, Wt, BSA)	X	Daily during drug administration in course 1, then weekly during course 1, then prior to each course of therapy	X
CBC, Differential, platelets	X	q.o.d. during drug administration, then weekly	X
Electrolytes, BUN, creatinine	X	weekly	X
PT/PTT	X	every 2 courses	
Ca ⁺⁺ , Mg ⁺⁺ , PO ₄ , uric acid, LDH	X	prior to each course	X
Urinalysis	X	prior to each course	X
SGPT, bilirubin (T/D), total protein, albumin,	X	prior to each course	X
Chest X-ray or appropriate imaging studies ⁺ ;	X	every 2 courses	X
BMA/BX [*]	X	day 21* of cycle 1 and day 21 of cycle 2	
Lumbar puncture	X	See section 6.0	
Pharmacokinetic Studies	See section 5.3		
Creatinine clearance or GFR [@]	X		

* If physical examination or CBC suggest no response, a bone marrow aspirate will be performed on day 14. Otherwise bone marrow aspirate will be performed at day 21. Patients will have bone marrow aspiration at week 3 and week 6 (i.e. day 21 of cycle 1 and day 21 of cycle 2). If the week 6 BMA is the first to document CR (e.g. week 3 BMA showed PR or was hypoplastic), BMA must also be performed at week 9 to confirm CR. Mail bone marrow slides for prestudy, week 3, 6, and 9, if done, in one batch to _____ Glaxo Wellcome, 5 Moore Drive, RTP, NC 27709. Tel # _____

— Use Airborne Express and mark shipping document "bill receiver".

+ CT or MRI for patients with bulky disease. The same imaging modality must be used throughout the course of the study. Baseline studies should be obtained not more than 7 days prior to the first treatment course.

@ When feasible, creatinine clearance or GFR should be obtained prior to the first course, even if the serum creatinine is normal.

3.1.1.3 Efficacy Measures

The pediatric oncology group's protocol for this study stated that the primary efficacy analysis would be the assessment of the early partial (or better) marrow response rate at day 21 of treatment. An early partial marrow response required $\leq 25\%$ bone marrow blasts and an early complete marrow response required $\leq 5\%$ bone marrow blasts at day 21.

Table 2 gives the criteria associated with each of three degrees of response to treatment.

Table 2 PGAA 2001: Response Criteria – ALL in Childhood

CATEGORY	RATING		
	1	2	3
Bone marrow Blasts - %	0 - 5	> 5 - 25	> 25
Hemogram:			
Hg g/dl	< 2 yr = ≥ 10	≥ 7	< 7
Hg g/dl	> 2 yr = ≥ 11	≥ 7	< 7
Neut. Gran/ μ l	> 1500	$\geq 500 - 1,500$	< 500
Blasts %	0	≤ 5	> 5
Platelets/ μ l	> 100,000	25,000 - $\leq 100,000$	< 25,000
Physical findings:			
Liver	Normal for age	\leq To umbilicus	Below umbilicus
Spleen	Normal for age	Abnormal	Grossly visible
Other	Normal for age	Definite	Marked
Symptoms/Performance			
Symptoms	Asymptomatic	Moderately symptomatic	Marked symptomatic
Performance	Normal activity	< 50% time in bed	$\geq 50\%$ time in bed

Complete remission of CNS defined as 2 Lumbar punctures (LP's) one week apart with 0 blasts identified.

Complete Response (CR) – A rating of 1 in all categories (M1, H1, P1, S1). The duration of CR lasts from the 1st day that CR is attained until the last day of CR.

Partial Response (PR)- A rating of 2 in one or more category but no rating of 3 in any category

Improvement (IMP)- Improvement of M, H, and/or P to a rating of 1 or 2 with 1 or more categories remaining at a rating of 3.

No response (NR)- No changes in any category

Progressive Disease - Deterioration from an initial disease status of 1 or 2.

To qualify for CR, subjects must have had a bone marrow blasts percentage of less than 5, no physical disease findings and full hematologic recovery (i.e., ANC >1500/ μ l, 0 peripheral blood blasts, platelets >100,000/ μ l and Hgb ≥ 10 g/dl, HgB ≥ 11 g/dl if ≥ 2 years of age).

3.1.1.4 Study Design and Sample size

A two-stage accrual model was planned for both Stratum 01 and Stratum 02. These strata were designed to decide between two pre-specified hypotheses about the probability of an early marrow complete response (EmCR) or early marrow partial response (EmPR). An early marrow response was based on the bone marrow blast percent at day 21 of cycle 1. The null hypothesis of a response rate (EmCR+EmPR) of 15% was tested against the alternative hypothesis of a response rate of 35%.

The purpose of the two-stage accrual model was to provide an opportunity to stop accrual early if the response rate at the end of Stage 1 was very low. If there were 4 or fewer responders from the first 20 evaluable subjects enrolled at the dose of 650 mg/m² in either Stratum 01 or 02, that stratum would have been closed to accrual and the data would have supported the null hypothesis. Under the null hypothesis of a true response rate of at most 15%, the probability of stopping the trial early was at least 60%.

The two stage design was amended a few times.

The June 2, 1997 protocol stipulated that there would be 15 patients (per stratum) in each stage and at least one PR or CR was needed in stage 1 to proceed to stage 2. Furthermore, the drug would be considered active if at least 3 of 30 patients achieved an early PR or CR.

The May 29, 1998 revision of the two stage design had the following characteristics:
stage 1: 20 patients in first stage; at least 5 early CR or PR to continue to second stage.
stage 2 : 17 additional patients; consider drug "active" if at least 11 of 37 achieve an early partial marrow response by day 21.

With this design, the probability of concluding that $p > .2$ when in reality $p \leq .2$ is .094.

The probability of concluding that $p > .2$ when in reality $p \geq .4$ is .90.

In the application GlaxoSmithKline has shifted the focus of efficacy from the early PR+CR rate to the rate of ever attaining a complete response (CR) or CR*(CR without hematologic recovery).

3.1.1.5 Patient Demographics

Most subjects in the Stratum 01 650 mg/m² dose group were male (87%, 27/31) and most were white (61%, 19/31). Fifty-eight (18/31) percent of subjects ranged in age from 3-12 years (overall mean, 11.56 years) at the time of enrollment, and the mean age at the time of initial diagnosis was 9.99 years.

Most subjects in the Stratum 02 650 mg/m² dose group were male (64%, 25/39) and most were white (64%, 25/39). Fifty-four (21/39) percent of subjects ranged in age from 3-12 years (overall mean, 11.45 years) at the time of enrollment, and the mean age at the time of initial diagnosis was 10.10 years.

Demographic characteristics were also summarized by assigned dose. For the 650 mg/m² dose group, most subjects were male (74%, 62/84) and most were white (62%, 52/84). Fifty-two (44/84) percent of subjects ranged in age from 3-12 years (overall mean, 11.93 years), and the mean age at time of initial diagnosis was 10.43 years.

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Table 3 PGAA2001: Summary of Demographic Characteristics (Strata 1 and 2)

	Number (%) of Subjects					
	Stratum 01			Stratum 02		
	650 mg/m ² N=31	900 mg/m ² N=6	Total N=37	650 mg/m ² N=39	900 mg/m ² N=9	Total N=48
Age Group , n (%)						
2mo – 2yrs	0	1 (17)	1 (3)	2 (5)	1 (11)	3 (6)
3 – 12yrs	18 (58)	3 (50)	21 (57)	21 (54)	5 (56)	26 (54)
13 – 16yrs	9 (29)	1 (17)	10 (27)	10 (26)	1 (11)	11 (23)
17 – 21yrs	4 (13)	1 (17)	5 (14)	6 (15)	2 (22)	8 (17)
Age (years)						
Mean	11.56	10.51	11.39	11.45	10.33	11.24
Minimum - Maximum	3.2-21.7	0.6-18.7	0.6-21.7	2.5-20.0	1.8-19.7	1.8-20.0
Sex, n (%)						
Female	4 (13)	2 (33)	6 (16)	14 (36)	5 (56)	19 (40)
Male	27 (87)	4 (67)	31 (84)	25 (64)	4 (44)	29 (60)
Race, n (%)						
White	19 (61)	3 (50)	22 (59)	25 (64)	6 (67)	31 (65)
Black	6 (19)	2 (33)	8 (22)	3 (8)	2 (22)	5 (10)
Hispanic	5 (16)	1 (17)	6 (16)	7 (18)	1 (11)	8 (17)
Asian	1 (3)	0	1 (3)	2 (5)	0	2 (4)
Other	0	0	0	2 (5)	0	2 (4)

Eighty-nine percent (33/37) of subjects in Stratum 01 and 73% (35/48) of subjects in Stratum 02 had a diagnosis of ALL. For both strata the majority of these subjects were in the 650 mg/m² dose group. Thirty percent (11/37) of subjects in Stratum 01 and 56% (27/48) of subjects in Stratum 02 achieved less than complete remission in response to their most recent prior induction.

In Stratum 03, most subjects were male (75%, 24/32) and most were white (63%, 20/32). Fifty-nine (19/32) percent of subjects ranged in age from 3-12 years (overall mean, 10.48 years) at the time of enrollment, and the mean age at the time of initial diagnosis was 9.49 years.

In Stratum 04, most subjects were male (76%, 26/34) and most were white (65%, 22/34). Thirty-eight (13/34) percent of subjects ranged in age from 13-16 years and 32% (11/34) of subjects ranged in age from 3-12 years (overall mean, 13.31 years) at the time of enrollment, and the mean age at the time of initial diagnosis was 11.77 years.

Sixty-six (21/32) percent of subjects in Stratum 03 had a diagnosis of ALL. In Stratum 04, 79% (27/34) percent of subjects had a diagnosis of LBL. Forty-seven percent (15/32) of subjects in Stratum 03 and 32% (11/34) of subjects in Stratum 04 achieved less than complete remission in response to their most recent prior induction.

When summarized by assigned dose, in the 650 mg/m² dose group 77% (65/84) of subjects had a diagnosis of ALL and 23% (19/84) of subjects had a diagnosis of LBL. Forty-four percent (37/84) of subjects in the 650 mg/m² dose group achieved less than

complete remission in response to their most recent prior induction.

Table 4 PGAA 2001: Diagnosis at Baseline and Response to Most Recent Induction (Strata1 and 2)

	Number (%) of Subjects					
	Stratum 01			Stratum 02		
	650 mg/m ² N=31	900 mg/m ² N=6	Total N=37	650 mg/m ² N=39	900 mg/m ² N=9	Total N=48
Diagnosis at Baseline						
Acute lymphoblastic leukemia	28 (90)	5 (83)	33 (89)	31 (79)	4 (44)	35 (73)
Lymphoblastic Lymphoma	3 (10)	0	3 (8)	8 (21)	5 (56)	13 (27)
Other ^a	0	1 (17)	1 (3)	0	0	0
Response to Most Recent Induction Therapy						
Failure/Less than complete remission	9 (29)	2 (33)	11 (30)	22 (56)	5 (56)	27 (56)
Complete Remission	20 (65)	4 (67)	24 (65)	17 (44)	3 (33)	20 (42)
Unknown	2 (6)	0	2 (5)	0	1 (11)	1 (2)

Table 5 shows what types of prior therapies patients had. For Stratum 01 all subjects received prior chemotherapy; in the 650 mg/m² dose group, 29% (9/31) received prior radiation and 19% (6/31) had prior surgery. For Stratum 02 all subjects received prior chemotherapy; in the 650 mg/m² dose group: 64% (25/39) received prior radiation and 18% (7/39) had prior surgery.

Table 5 PGAA 2001: Summary of Prior Anti-Cancer Therapies by Modality (Strata-1 and 2)

Type of Prior Therapy	Number (%) of Subjects					
	Stratum 01			Stratum 02		
	650 mg/m ² N=31	900 mg/m ² N=6	Total N=37	650 mg/m ² N=39	900 mg/m ² N=9	Total N=48
Chemotherapy	31 (100)	6 (100)	37 (100)	39 (100)	9 (100)	49 (100)
Radiation	9 (29)	1 (17)	10 (27)	25 (64)	8 (89)	33 (69)
Surgery	6 (19)	1 (17)	7 (19)	7 (18)	5 (56)	12 (25)

Prior Inductions

Prior to GSK analyses, subjects were allocated to a stratum based on the number of prior inductions reported by investigators on the COG Prestudy Form. All subjects in Stratum 01 were reported to have received one prior induction and all subjects in Stratum 02 were reported to have received more than 1 prior induction. Table 6 gives the distribution of the number of prior inductions in stratum 02.

Table 6 PGAA 2001: Stratum 02 Number of Prior Inductions

Prior Inductions	Stratum 02		
	650 mg/m ² N=39	900 mg/m ² N=9	Total N=48
2	27 (69)	2 (22)	29 (60)
3	7 (18)	5 (56)	12 (25)
4	2 (5)	2 (22)	4 (8)
5	2 (5)	0	2 (4)
Unknown	1 (3)	0	1 (2)

Study population, safety and efficacy data were summarized using the all treated subjects population. This consists of all subjects who received at least one dose of study drug.

Prior Stem Cell Transplants

For Stratum 01, in the 650 mg/m² dose group, 6% (2/31) of subjects had prior stem cell transplants; one subject received an allogeneic bone marrow stem cell transplant, and one subject had both prior allogeneic and autologous bone marrow stem cell transplants.

For Stratum 02, in the 650 mg/m² dose group, 21% (8/39) of subjects had prior stem cell transplants; 13% (5/39) of subjects had prior allogeneic bone marrow stem cell transplants (one of these subjects also had another stem cell transplant but the source is unknown), one other subject had an allogeneic transplant of unknown type, and 5% (2/39) of subjects had prior autologous bone marrow stem cell transplants.

3.1.1.6 Sponsor's Results

To qualify for CR, subjects must have had no evidence of disease ($\leq 5\%$ bone marrow blasts and no extramedullary disease) and full hematologic recovery as defined in the protocol (i.e., ANC $>1500/\mu\text{l}$, 0% peripheral blood blasts, platelets $>100,000/\mu\text{l}$ and Hgb $\geq 10\text{g/dl}$ or HgB $\geq 11\text{g/dl}$ if ≥ 2 years of age). To qualify for a CRh* subjects must have had no evidence of disease and hematologic recovery to at least retreatment levels (ANC $>500/\mu\text{l}$, platelets $>50,000/\mu\text{l}$, and Hgb $\geq 7\text{g/dl}$). To qualify for CR*, subjects must have had no evidence of disease with or without hematologic recovery. To be evaluable for a GSK marrow response, subjects were to have a baseline bone marrow blast percent of at least 25%. To qualify for mCR, subjects must have had bone marrow blasts of $<5\%$.

Table 7 shows the response rates as determined by the sponsor.

For the Stratum 02 650 mg/m² dose group, 13% (5/39) of subjects achieved a CR (95% CI: 4%, 27%). An additional 3 subjects had no evidence of disease and had recovery of platelets, ANC and hemoglobin to retreatment levels (CRh*), but did not have full hematologic recovery. Subject 1062 did not reach full recovery of platelets or Hgb. Subject 1131 did not reach full recovery of ANC, platelets or Hgb. Subject 1109 actually did achieve hematologic full recovery levels 23 days after achieving a CRh*, however, the following day her percent bone marrow blasts were $>25\%$, so she was not considered

in remission long enough to claim a CR. One additional subject (1068) did not recover to retreatment levels of ANC or platelets but did achieve a CR*. Subject 1032 did not achieve CR*, as he did not have complete resolution of abdominal and pelvic lymphadenopathy.

For the Stratum 01 650 mg/m² dose group 42% (13/31) of subjects achieved a CR (95% CI: 25%, 61%). An additional 2 subjects had no evidence of disease and had recovery of platelets, ANC and hemoglobin to retreatment levels (CRh*), but not full recovery. Subject 1040 did not reach full recovery of ANC, and Subject 1074 did not reach full recovery of ANC or Hgb. All 15 subjects that achieved a CRh* were also noted to have achieved CR* and GSK mCR.

Table 7 PGAA 2001: Response Rates by Stratum and Dose (Sponsor's Results)

	Number (%) of Subjects					
	Stratum 01			Stratum 02		
	650 mg/m ² N=31	900 mg/m ² N=6	Total N=37	650 mg/m ² N=39	900 mg/m ² N=9	Total N=48
GSK Marrow Response	(n=31)	(n=5)	(n=36)	(n=36)	(n=8)	(n=44)
GSK Marrow CR 95% CI	15 (48) [30, 67]	2 (40) [5, 85]	17 (47) [30, 65]	10 (28) [15, 45]	2 (25) [3, 65]	12 (27) [15, 43]
GSK Marrow PR	1 (3)	0	1 (3)	2 (6)	0	2 (5)
GSK Marrow Response* 95% CI	16 (52) [33, 70]	2 (40) [5, 85]	18 (50) [33, 67]	12 (33) [19, 51]	2 (25) [3, 65]	14 (32) [19, 48]
Less Than GSK Marrow PR	15 (48)	3 (60)	18 (50)	24 (67)	6 (75)	30 (68)
CR* Response	(n=31)	(n=6)	(n=37)	(n=39)	(n=9)	(n=48)
CR* (CR w/o hematologic recovery) 95% CI	15 (48) [30, 67]	2 (33) [4, 78]	17 (46) [29, 63]	9 (23) [11, 39]	3 (33) [7, 70]	12 (25) [14, 40]
<CR* (CR w/o hematologic recovery)	16 (52)	4 (67)	20 (54)	30 (77)	6 (67)	36 (75)
CRh* Response	(n=31)	(n=6)	(n=37)	(n=39)	(n=9)	(n=48)
CRh* 95% CI	15 (48) [30, 67]	2 (33) [4, 78]	17 (46) [29, 63]	8 (21) [9, 36]	3 (33) [7, 70]	11 (23) [12, 37]
<CRh*	16 (52)	4 (67)	20 (54)	31 (79)	6 (67)	37 (77)
Complete Response	(n=31)	(n=6)	(n=37)	(n=39)	(n=9)	(n=48)
Complete Response (CR) 95% CI	13 (42) [25, 61]	1 (17) [0, 64]	14 (38) [22, 55]	5 (13) [4, 27]	2 (22) [3, 60]	7 (15) [6, 28]
Less Than Complete Response (<CR)	18 (58)	5 (83)	23 (62)	34 (87)	7 (78)	41 (85)

Independent Review

Subject 1109 was reported to have 2% bone marrow blasts by the primary institution and 12% by independent review. Subject 1132 was determined by the primary institution to have 5% bone marrow blasts and to have 7% bone marrow blasts by independent review. Thus, two mCR subjects per COG would be interpreted to have less than a mCR per independent review (1109, 1132).

Duration of Response

Duration of response was measured from the date of response to the earliest of

progression, death, or last contact. Quartile estimates and their 95% confidence intervals were done according to the Product-Limit Method (i.e., Kaplan-Meier). Confidence intervals were computed based on the sign test.

As shown in Table 8 durations of CR for the 650 mg/m² dose group ranged from 4.7 to 36.4 weeks for Stratum 02 and from 0.9 to at least 260 weeks for Stratum 01.

Reviewer's Comment:

Stratum 02 650 mg/m² subjects 1039, 1131, and 1132 received stem cell transplants after nelarabine therapy. The duration of CR or CR for non-transplanted patients in this group ranged from 3.3 to 41.9 weeks.*

In the stratum 01 650 mg/m² group only subjects 1040, 1123, and 1124 did not receive stem cell transplants after nelarabine therapy. The duration of CR or CR for non-transplanted patients in this group ranged from 1.4⁺ to 33.1 weeks.*

Table 8 PGAA 2001: Duration of CR for Individual Subjects (Strata 01 and 02 650 mg/m² dose) [Sponsor's Results]

Stratum Dose Group	Subject	Duration of CR (Weeks)
01 / 650	1024	2.3
	1034	234.3
	1042	260.0+
	1140	133.6+
	1078	190.6+
	1076	207.0
	1069	0.9
	1123	2.9
	1065	23.4
	1047	6.3
	1124	1.4+
	1049	229.6+
	1133	143.1+
02 / 650	1039	36.4
	1093	9.3
	1081	4.7
	1036	6.1
	1132	14.1

*Subject 1093 received IT methotrexate in cycle 4

Subject 1123 received triple intrathecal treatment in cycle 3

The time to CR for the 650 mg/m² dose groups for Strata 01 and 02 are presented in Table 9. For stratum 02 they ranged from 3.4 to 12.0 weeks and for stratum 01 they ranged from 2.7 to 17.6 weeks.

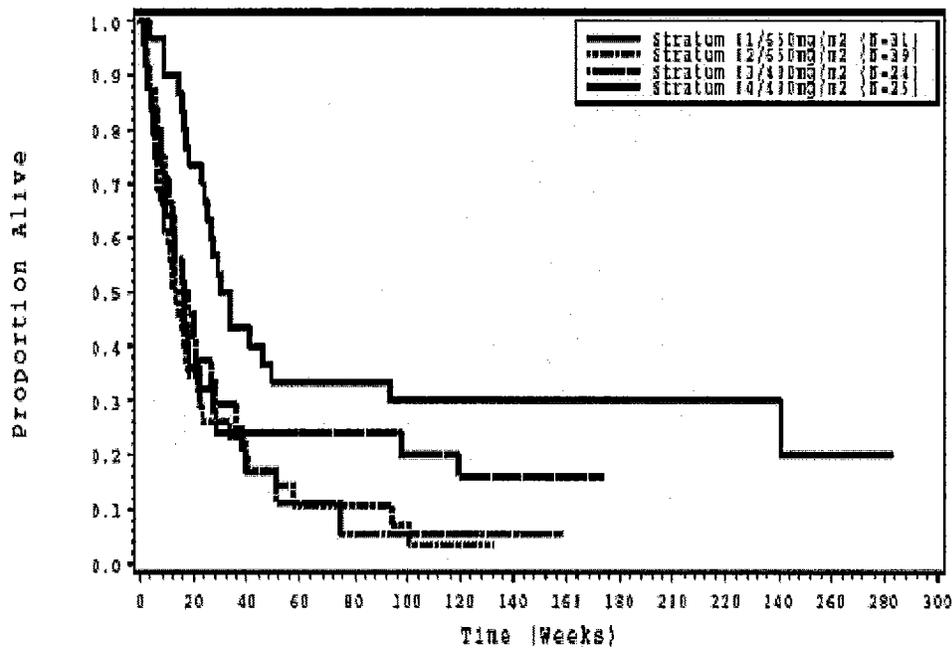
Table 9 PGAA 2001: Sponsor's Time to CR for Individual Subjects (Strata 01 and 02 650 mg/m² Dose Groups)

Stratum/ Dose Group	Subject	Time to CR (Weeks)
01/650	1024	5.9
	1034	6.4
	1042	2.7
	1140	3.7
	1078	6.0
	1076	3.3
	1069	17.6
	1123	9.4
	1065	3.7
	1047	6.1
	1124	6.6
	1049	5.3
	1133	3.7
02/650	1039	3.4
	1093	6.1
	1081	12.0
	1036	4.1
	1132	5.0

Overall Survival

The median overall survival for subjects in the 650 mg/m² dose group was 13.1 weeks (95% CI: 8.7, 17.4) for Stratum 02 and 33.3 weeks (95% CI: 24.1, 93.6) for Stratum 01.

Figure 1 PGAA 2001: Summary of Overall Survival (650 mg/m² and 400 mg/m² Dose Groups)



3.1.1.7 Sponsor's Efficacy Conclusions

Among subjects whose disease failed to respond to most recent prior induction attempt:

- For Stratum 02, 650 mg/m² dose group subjects whose disease failed to respond to their most recent prior induction, 18% (4/22) achieved a complete response with durations from 4.7 to 36.4 weeks.
- For Stratum 01, 650 mg/m² dose group subjects whose disease failed to respond to their most recent prior induction, 44% (4/9) achieved a complete response with durations from 0.9 to at least 207 weeks.
- Overall survival for subjects whose disease failed to respond to their most recent prior induction ranged from 14.6 to 100.4 weeks for the Stratum 02, 650 mg/m² dose group and from 18.3 to at least 210.1 weeks for the Stratum 01, 650 mg/m² dose group.
- The one year survival rate for Stratum 02 was 14% and for Stratum 01 it was 56%.

Among subjects with two or more prior inductions (Stratum 02) at the 650 mg/m² dose:

- For the Stratum 02, 650 mg/m² dose group, 13% (5/39) of subjects achieved a complete response (CR) with durations ranging from 4.7 to 36.4 weeks.
- The one year survival rate for Stratum 02 at the 650 mg/m² dose was 14%.

Survival ranged from 16.6 to 57.4 weeks among subjects who achieved a CR.

- Comparable marrow CR rates of 26% (9/35) and 25% (8/32) were assessed by COG and GSK, respectively, in subjects enrolled in the COG Stratum 02, 650 mg/m² dose group.

Among subjects with one prior induction (Stratum 01) at the 650 mg/m² dose:

- For the Stratum 01, 650 mg/m² dose group, 42% (13/31) of subjects achieved a complete response (CR) with durations ranging from 0.9 to at least 260 weeks.
- The one year survival rate for Stratum 01 at the 650 mg/m² dose was 33%.

Survival ranged from at least 7.9 to at least 262.6 weeks among subjects who achieved a CR.

- Comparable marrow CR rates of 46% (16/35), and 49% (17/35) were assessed by COG and GSK, respectively, in subjects enrolled in the COG Stratum 01, 650 mg/m² dose group.

Among Strata 01 and 02 subjects at the 650 mg/m² dose:

- The protocol defined endpoint of the study was early marrow response (EmCR + EmPR) as assessed by COG. For COG Stratum 02, 650 mg/m² dose group, 26% (9/35) of subjects achieved an overall early marrow response, five of whom achieved an EmCR. For COG Stratum 01, 650 mg/m² dose group, 49% (17/35) of subjects achieved an overall early marrow response, 10 of whom achieved an EmCR. Results, therefore, met the protocol's prespecified criteria for a positive study.

3.1.1.8 Reviewer's Results

The original protocol stated that the primary endpoint was the early marrow CR+PR rate at day 21. Eight of the first 20 stratum 1 patients achieved an early marrow PR or CR (5/8 had an early EmCR). Three more of the first 20 stratum 1 patients had an early mCR within a week of day 21. Three of the first 20 stratum 2 patients achieved an early marrow PR or CR (3/3 had an EmCR). Three more of the first 20 stratum 2 patients achieved an early marrow CR and one more had an early marrow PR within a week of day 21.

Table 10 PGAA 2001: Early Marrow Response Rates for First Stage of Study (first 20 patients)

TIME	STRATUM 1		STRATUM 2	
	Early MR	Early MR+PR	Early MR	Early MR+PR
by day 21	5 (25%) [9%, 49%]	8(40%) [19%, 64%]	3 (15%) [3%, 38%]	3(15%) [3%, 38%]
by day 28	8 (40%) [19%, 64%]	11 (55%) [32%, 77%]	6 (30%) [12%, 54%]	7(35%) [15%,59%]

Including the patients from the second stage, this reviewer found that 10/48 stratum 2 patients achieved an early marrow CR or PR (7 of the 10 were mCRs). Thus, in stratum 2 the early day 21 marrow CR rate was 14% (95% C.I.=[6%, 28%]) and the early day 21 marrow CR+PR rate was 21% (95% C.I.=[10%, 35%]).

It is recognized that the assessment of complete responses requires clinical judgment. For the record, this reviewer obtained some discrepancies with the sponsor’s results on the duration of response as determined by applying the strict criteria for CR or CR* and the criteria for relapse (bone marrow blasts > 5%, reappearance of disease, death) or censoring at last contact. In all but one of the following cases the FDA clinical reviewer agreed with the sponsor’s assessment of response. The net result is that stratum 2, 900 mg/m², patient 1004 classified as a strict CR by the sponsor would technically be a CR* in our view. Also, this reviewer differed from the sponsor on the duration of response for some patients as listed below.

- Subject 1004, LL diagnosis, Stratum 2, 900 mg/m²: Sponsor classified as CR but platelets never exceeded 50,000 (<100,000 needed for CR). Therefore, we believe this patient should be classified a CR* instead of a CR. Extramedullary sites that were abnormal at baseline were not documented normal later except by physical exam on day 16.
- Subject 1081, LL diagnosis, Stratum 2, 650 mg/m²: despite a steady rise platelets never quite reached CR level (98k < 100k) so technically the patient would be a CR* rather than a CR. However, the final count was deemed to be close enough to the limit so the patient was classified as a CR.
- Subject 1140, AL diagnosis, Stratum 1, 650 mg/m²: had high bone marrow blast pct 6 at week 15.7 (day 110) which technically gives a CR duration of 12.0 weeks but the sponsor reported a duration of 133.6 weeks. Also, the patient had a cord blood transplant at week 20 which confounds the effect of Nelarabine on the sponsor’s 133.6 week duration.
- Subject 1076, AL diagnosis, Stratum 1, 650 mg/m²: had high bone marrow blast pct (15) at week 51 (day 357) giving a CR duration of 44.7 weeks, but the sponsor reported a

duration of 207 weeks. There was another high marrow blast pct (8) at day 588. Ignoring the first high blast gives a CR duration of 77.7 weeks. Despite these two high marrow blasts percentages the patient did have 4 marrows with <5% blasts after the first abnormal marrow.

- Subject 1133, AL diagnosis, Stratum 1, 650 mg/m2: had a high bone marrow blast pct (20) at week 5.7 (day 40) which would give a CR duration of 2.0 weeks but the sponsor got a duration of 143 weeks.
- Subject 1040, AL diagnosis, Stratum 1, 650 mg/m2: CR*, my duration: 18 weeks GSK: 33 weeks
- Subject 1132, AL diagnosis, Stratum 2, 650 mg/m2: lowest bone marrow blasts percentage was 5 and this was found to be higher, 7, by the independent reviewer. The patient did have a steady increase in peripheral blood counts though which suggests that the patient was a CR.

Error! Reference source not found. shows the platelet values obtained from patient 1004 over time. Based on the available data it is clear that they never exceeded the 100,000/UL level required for a strict complete response.

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Figure 2 PGAA 2001: Patient 1004's Lab values for Platelets and Bone Marrow Blasts

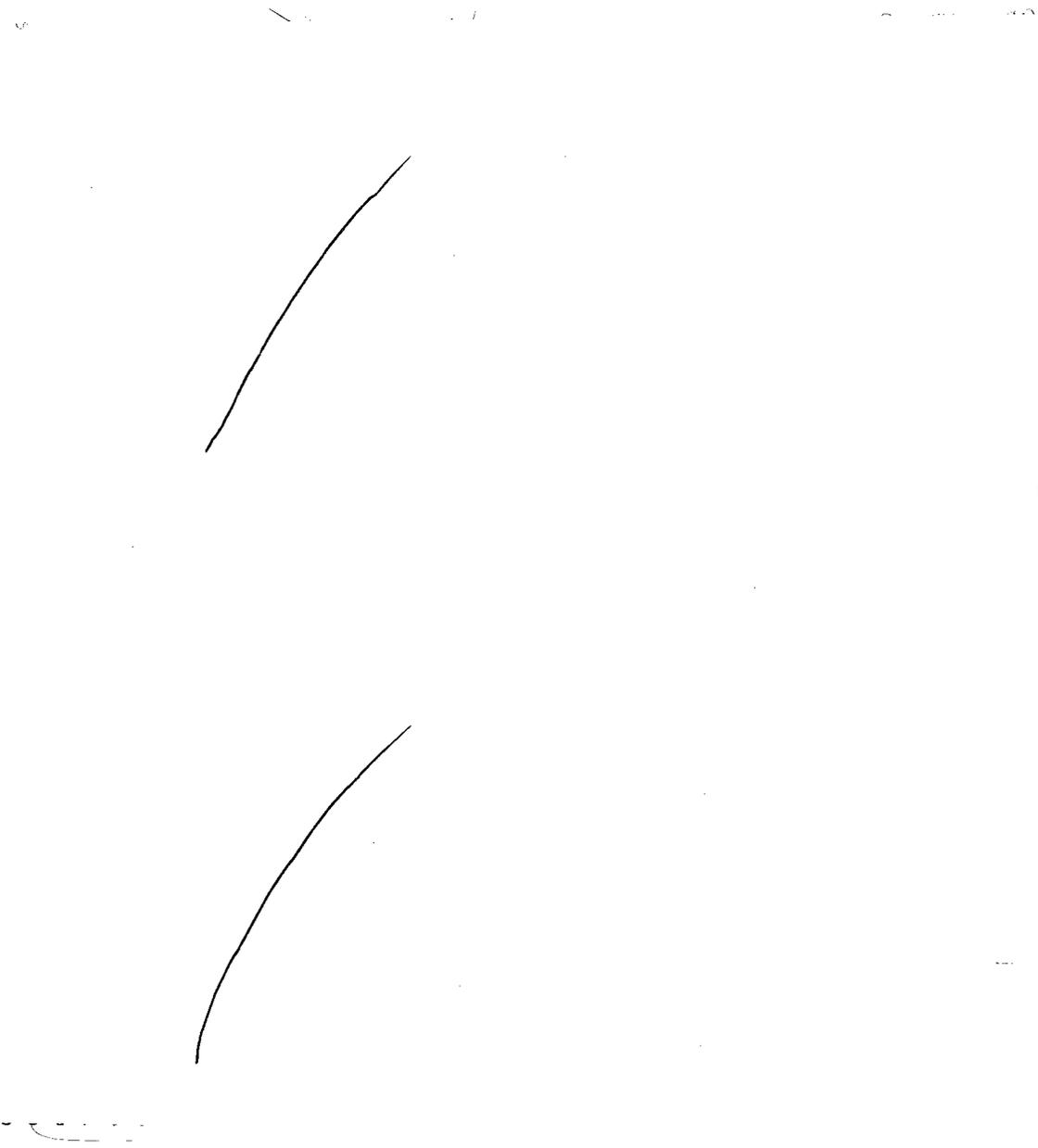


Table 11 shows the CR and CR* (CR w/out hematologic recovery) rates confirmed by the FDA reviewers on the basis of the available data.

Table 11 PGAA 2001: CR and CR* rates for stratum 01 and stratum 02

	STRATUM 1			STRATUM 2		
Response	650 mg N=31	900 mg N=6	All N=37	650 mg N=39	900 mg N=9	All N=48
CR	13 (42) [25, 61]	1 (17) [0, 64]	14 (38) [22, 55]	5 (13) [4, 27]	1 (11) [0, 48]	5 (10) [3, 23]
CR*	2 (6) [0, 21]	1 (17) [0, 64]	3 (8) [2, 22]	4 (10) [3, 24]	2 (22) [3, 60]	7 (15) [6, 28]
CR+CR*	15 (48) [30, 67]	2 (33) [4, 78]	17 (46) [29, 63]	9 (23) [11, 39]	3 (33) [7, 70]	12 (25) [14, 40]

Among those patients that attained a CR or CR* the median time to best response (CR or CR*) was 4.1 weeks (95% C.I.= [3.0, 5.7]). The range of times to CR or CR* was 2 to 8.6 weeks.

Some patients had transplants after Nelarabine therapy which confounds the effect of Nelarabine on their duration of response. Table 11 gives the response durations for non-transplanted patients that achieved a CR or CR*. As indicated in the table, some patients received additional intrathecal or systemic therapy. This confounds the effect of Nelarabine on their duration of response.

Table 12 PGAA 2001: Remission Duration of Non-transplanted Patients

Stratum 01	Stratum 02
Remission duration (weeks)	Remission duration (weeks)
33.1 (sys)*	42.1 (IT + sys)*
2.9	32.6 (IT)
1.4	9.3 (IT)
	6.1 (sys)*
	4.7
	3.6
	3.3

Because this was an open label, non-randomized, uncontrolled study no statistical comparisons could be made. Therefore, clinical judgment is needed to evaluate the efficacy of Nelarabine.

3.1.2 Study PGAA2002/CALGB19801

This study was initiated on October 7, 1998 and completed on June 15, 2002.

3.1.2.1 Study Design

This was an open-label, multicenter phase II study in adult subjects with refractory or relapsed T-lineage ALL or LBL. The study was conducted by CALGB as an inter-group trial in cooperation

with SWOG and affiliated institutions. Nelarabine was to be administered by intravenous (IV) infusion at a dose of 1500 mg/m² over 2 hours on days 1, 3, and 5 of a 21 day treatment cycle. The main entry criteria included adults (≥16 years) who were refractory to at least one induction treatment regimen or in first or later relapse after achieving a complete response. The study was opened at a dose of 2200 mg/m²/day but was amended to a dose of 1500 mg/m²/day to decrease the risk of neurologic toxicity. Three subjects received the 2200 mg/m² dose. Data from these subjects were included in all analyses.

This trial was designed to accrue a maximum of 35 evaluable patients, although with the two-stage design the trial could have been stopped early after the accrual of a minimum of 18 patients. With an estimated accrual rate of about 12-15 patients per year, it was expected that accrual would be completed in about 2.5 to 3 years. The major endpoint of this study was complete response rate. If the study concluded that the true response rate was at least 30% 506U78 (Nelarabine) would be considered for further research. On the other hand, if the data indicated that the true response rate was no better than 10%, then 506U78 would be considered to be inactive in the treatment of refractory or relapsed T-cell ALL and lymphoblastic lymphoma. Letting p = the probability of complete response, an optimal two-stage design was to be used to test the null hypothesis that $p \leq 10\%$ versus the alternative hypothesis that $p \geq 30\%$. With this design, accrual could have been stopped early to accept the null hypothesis that the drug was inactive. In the first stage of the design, 18 evaluable patients were to be accrued, and if 2 or less patients responded, the trial was to be closed with acceptance of the null hypothesis. If 3 or more of the 18 patients responded, an additional 17 evaluable patients were to be accrued (for a total of 35 patients). If 6 or less (17%) of these 35 patients responded, the null hypothesis was to be accepted and 506U78 was to be considered inactive. If 7 or more (20%) of these patients responded, the null hypothesis was to be rejected in favor of the alternative hypothesis that the true response rate was $\geq 30\%$. This design has Type I and II error rates of 0.05 and 0.10, respectively. If the observed response rate was 30%, the 95% confidence interval would have a half-width of 0.15. If the response rate was 20% the half-width of the confidence interval would be 0.13.

3.1.2.2 Efficacy Measures

The assessment of response after treatment for acute leukemia requires a physical examination, complete blood count, platelet count, differential count, and bone marrow aspiration and biopsy. Extramedullary sites known to be involved by leukemia prior to treatment (e.g., mediastinal lymphadenopathy or CSF) must be reexamined as well. Immunophenotyping, cytochemistry, and cytogenetic analyses could be supportive data but were not required for clinical assessment. The response had to be maintained for one month in order to be considered valid; patients who proceeded with additional chemotherapy had to have no evidence of disease recurrence during this one month interval.

The protocol defined primary endpoints were response rate (i.e., CR and PR) and response duration.

CALGB Complete Response (CR):

- For ALL patients: absolute neutrophil count (segs and bands) >1500/μL, no circulating blasts, platelets >100,000/μL, bone marrow cellularity >20% with trilineage hematopoiesis, and <5%

marrow blast cells, none of which appear neoplastic. All previous extramedullary manifestations of disease were to be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement). Because chemotherapy can produce prolonged cytopenias, subjects who did not recover normal peripheral blood counts but also did not relapse within 6 months of their final chemotherapy treatment could be considered retrospectively to have achieved a CR starting one month after their last transfusion.

- For LBL Patients: disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor and appearance of no new lesions.

Relapsed Disease -The reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (i.e., >5%) or in the CNS (positive cytopsin examination of CSF) or in any other extramedullary site after a CR; or progression to >25% leukemia blasts cells in the marrow after a PR.

3.1.2.3 Patient Demographics

Table 13 shows patient demographic characteristics at baseline. Twenty-eight subjects (72%) had undergone ≥ 2 prior attempts at induction and 11 (28%) had received 1 prior induction. Most subjects were male (82%) and most were white (69%). Median and mean age at the time of study entry were 34 and 35 years, respectively. The age range was 16 to 66 years for all treated subjects and 16 to 65 years for subjects with ≥ 2 prior inductions. Thirty three subjects (85%) were >21 years of age at the time of enrollment.

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Table 13 PGAA2002 Patient Demographic Characteristics by Number of Prior Inductions

n (%)		1 Prior Induction (N=11)	≥ 2 Prior Inductions (N=28)	Total (N=39)
Age Group				
	16-21	0	6 (21)	6 (15)
	22-64	10 (91)	21 (75)	31 (79)
	≥65	1 (9)	1 (4)	2 (5)
Age (yrs.)				
	Mean	37.5	34.0	35.0
	SD	15.94	12.60	13.51
	Median	30.0	34.0	34.0
	Minimum	23	16	16
	Maximum	66	65	66
Age at Initial Diagnosis (yrs.)				
	Mean	36.1	31.5	32.8
	SD	15.95	11.91	13.12
	Median	30.0	31.5	30.0
	Minimum	21	16	16
	Maximum	66	64	66
Sex				
	Male	9 (82)	23 (82)	32 (82)
	Female	2 (18)	5 (18)	7 (18)
Race				
	Caucasian	10 (91)	17 (61)	27 (69)
	African American	0	9 (32)	9 (23)
	Native American	1 (9)	0	1 (3)
	Hispanic	0	1 (4)	1 (3)
	Oriental	0	1 (4)	1 (3)
Height (cm)				
		(n=11)	(n=28)	(n=39)
	Mean	174.9	173.6	174.0
	SD	12.06	9.55	10.17
	Median	178.0	173.5	175.0
	Minimum	148	154	148
	Maximum	188	191	191
Weight (kg)				
		(n=11)	(n=26)	(n=37)
	Mean	83.5	81.2	81.9
	SD	10.58	19.44	17.16
	Median	83.0	82.0	82.0
	Minimum	70	54	54
	Maximum	103	144	144

A majority of subjects (72%) were CALGB Performance Status (PS) 0 or 1 at baseline. Six subjects (15%) were PS 2 and five subjects (13%) were PS 3. Table 14 shows that twenty-six subjects (67%) had extramedullary disease at baseline and one subject's status was unknown. A history of CNS leukemia was reported for only 4 subjects (11%).

Table 14 PGAA 2002: Summary of Extramedullary Disease at Baseline and History of CNS Leukemia by Number of Prior Inductions (All Treated Subjects)

n (%)		1 Prior Induction (N=11)	≥ 2 Prior Inductions (N=28)	Total (N=39)
Extramedullary Disease at Baseline				
Yes		6 (55)	20 (71)	26 (67)
No		5 (45)	7 (25)	12 (31)
Unknown		0	1 (4)	1 (3)
History of CNS Leukemia				
No		11 (100)	24 (86)	35 (90)
One Occurrence		0	3 (11)	3 (8)
> One Occurrence		0	1 (4)	1 (3)

Table 15 shows the number of patients with T-ALL and T-LBL diagnoses and also the number of responses to the most recent induction. Sixty-seven percent of subjects (26/39) had ALL and 33% had LBL. Nineteen of the 39 treated subjects (49%) had disease that failed to respond to the most recent prior induction attempt. Of the 28 subjects with ≥2 prior inductions, seventeen (61%) did not achieve a complete response with the most recent induction attempt.

Table 15 PGAA 2002: Summary of Diagnosis at Baseline and Response to Most Recent Induction by Number of Prior Inductions (All Treated Subjects)

n (%)		1 Prior Induction (N=11)	≥ 2 Prior Inductions (N=28)	Total (N=39)
Diagnosis	ALL	9 (82)	17 (61)	26 (67)
	LBL	2 (18)	11 (39)	13 (33)
Response to Most Recent Induction				
	Complete Response	9 (82)	11 (39)	20 (51)
	Failure (less than Complete Response)	2 (18)	17 (61)	19 (49)

A summary of prior anti-cancer therapies is presented in Table 16. All treated subjects had received prior chemotherapy. The most common prior chemotherapy agents were vincristine, cytarabine, cyclophosphamide and methotrexate. Four (14%) patients with 2 or more prior inductions and 1 (9%) of the patients with 1 prior induction had a bone marrow transplant as a prior therapy.

Table 16 PGAA 2002: Summary of Prior Therapies by Number of Prior Inductions (All Treated Subjects)

Type n (%)	1 Prior Induction (N=11)	≥ 2 Prior Inductions (N=28)	Total (N=39)
Total	10 (91) ^a	27 (96) ^b	37 (95) ^b
Chemotherapy	10 (91)	27 (96)	37 (95)
Limited Radiation (<50% portion of body)	1 (9)	8 (29)	9 (23)
Extensive Radiation (≥50% portion of body)	1 (9)	4 (14)	5 (13)
Bone Marrow Transplant	1 (9)	4 (14)	5 (13)
Surgery	1 (9)	2 (7)	3 (8)
Immunotherapy	0	2 (7)	2 (5)

Data Source: Section 13, Table 13.4

a. As presented on the CALGB Prior Therapy Form

b. Although all treated subjects received prior chemotherapy, subjects 82761 and 76143 are not included in this table as the corresponding CRF (Prior Therapy Form) was not submitted for these subjects.

3.1.2.4 Sponsor's Results

As seen in Table 17 a total of 7 subjects (18%) experienced a complete response based on GSK's assessment. Five of these seven had received ≥ 2 prior inductions and 2 had received 1 prior induction. The GSK complete response rate was, therefore, 18% for each sub-population. A total of 11 subjects (28%) experienced a complete response based on CALGB's assessment. Seven of these subjects had received ≥ 2 prior inductions. Therefore, the CALGB complete response rate in subjects with ≥ 2 prior inductions was 25%. The difference between CALGB and GSK complete response percentages is mainly due to lack of required documentation of hematologic recovery or documentation of resolution of extramedullary disease for four subjects (76579, 84144, 76143 and 82970).

At an alpha of 7%, the CR rate provides evidence that the null hypothesis of a true response rate $\leq 10\%$ should be rejected in favor of the alternative hypothesis that the true response rate is $\geq 30\%$.

Table 17 PGAA 2002: GSK and CALGB Response Rates by Number of Prior Inductions

	1 Prior Induction (N=11)	≥2 Prior Inductions (N=28)	Total (N=39)
GSK Complete Response (CR)	2 (18)	5 (18)	7 (18)
[95% CI]	[2, 52]	[6, 37]	[8, 34]
Less than a Complete Response (<CR)	9 (82)	23 (82)	32 (82)
CALGB Complete Response (CR)	4 (36)	7 (25)	11 (28)
[95% CI]	[11, 69]	[11, 45]	[15, 45]
Partial Response (PR)	2 (18)	3 (11)	5 (13)
Less than Partial Response (<PR)	5 (45)	18 (64)	23 (59)

Of the 26 subjects with ALL, 8 (31%) had a CR by CALGB criteria, and 4 of those 8 experienced a CR using GSK criteria. All 4 of the subjects with CR by GSK criteria also had their CR confirmed via bone marrow exam one month later. Of the 4 subjects with CR by CALGB but not GSK criteria, 2 (76143 and 84144) were assigned a CR* by GSK because they did not have required documentation of hematologic recovery. Two subjects (82970 and 76579) did not have required documentation of extramedullary disease resolution to be assigned a CR and were assigned a mCR. Three of the 13 subjects (23%) with LBL experienced a complete CR by both CALGB and GSK criteria. All of these CRs were confirmed one month later.

Nine of the 39 treated subjects had a complete response with no evidence of disease with or without hematologic recovery (CR*). Of the 9, 7 subjects went on to achieve a complete response with full hematologic recovery (CR). Two of the 9 did not have documented evidence of full hematologic recovery and were classified as having a CR*. One of these subjects had received one prior induction (84144) and the other ≥ 2 prior inductions (76143). Subject 84144 withdrew from protocol treatment without demonstrating platelet and absolute neutrophil count (ANC) recovery in order to receive a cord blood transplant. Subject 76143 experienced full hematologic recovery but subsequently relapsed 17 days later. The response in this subject was not classified as a CR by GSK because it was not maintained for 1 month.

Of the 28 subjects with ≥ 2 prior inductions, 1 had a complete response but never had documented evidence of full hematologic recovery. An additional 5 subjects in this group achieved a CR* and subsequently had documentation of full hematologic recovery. Thus, a total of 6 subjects with ≥ 2 prior inductions achieved a CR*. A summary of complete response with or without hematologic recovery is presented in Table 18.

Table 18 PGAA 2002: Summary of Complete Response With or Without Hematologic Recovery (CR+CR*) by Number of Prior Inductions (All Treated Subjects)

	1 Prior Induction (N=11)	≥ 2 Prior Inductions (N=28)	Total (N=39)
Complete Response w/ or w/o Hematologic Recovery (CR+CR*)	3 (27)	6 (21)	9 (23)
[95% CI]	[6, 61]	[8, 41]	[11, 39]
Less than CR*	8 (73)	22 (79)	30 (77)

Duration of Response

Table 19 shows the duration of response for patients with a marrow CR, CR*, or strict CR. The range (minimum to maximum) for duration of GSK CR was 15.1 to 212.0 weeks. The range for duration of GSK CR* was 4 to 215 weeks. Duration of GSK mCR (for individual subjects with bone marrow involvement at baseline) ranged from 4 to 217.1 weeks. The range for duration of CALGB CR was also 4.0 to 217.1 weeks. One subject (79729) proceeded directly to high-dose therapy with BMT while still in a nelarabine-induced remission and remained in a CR for 156.3+ weeks. One subject (78326) remained in a prolonged CR (195.4+ weeks) without subsequent anti-cancer therapy following treatment with 3 cycles of nelarabine. Prior to enrollment, this subject had relapsed following surgical resection and two multi-agent induction regimens, one of

which included autologous stem cell infusion. Subjects 79729 and 78326 were still in remission at the date of last contact.

Table 19 PGAA 2002: Duration of CALGB and GSK Responses

Number of prior Inductions	Subject	CALGB CR (Weeks)	GSK mCR (Weeks)	GSK CR* (Weeks)	GSK CR (Weeks)
1 Prior Induction	77661	217.1	217.1	215.0	212.0
	82761	55.9	n/a	53.4	51.0
	76579	6.0	6.0	n/a	n/a
	84144	4.7	4.7	4.7	n/a
≥2 Prior Inductions	77798	26.6	18.9	18.9	18.9
	83908	15.1	15.1	15.1	15.1
	82137	30.1	n/a	30.1	29.4
	79729	156.0+	n/a	156.3+	156.3+
	78326	195.4+	n/a	195.4+	195.4+
	82970	18.1	17.7	n/a	n/a
	76143	4.0	4.0	4.0	n/a
	73718	n/a	4.3	n/a	n/a

Time to Response

Table 20 shows the time until response for patients with a marrow CR, CR*, or strict CR. The range (minimum to maximum) of time to GSK CR, CR* and mCR was 2.9 to 11.7 weeks for each. The range of time to CALGB CR was 2.7 to 7.6 weeks. Subject 77798 was considered to be a CR by CALGB at week 4, however, in GSK's review, the first available documentation of a bone marrow exam revealing <5% blasts was at 11.7 weeks.

Table 20 PGAA 2002: Time to GSK and CALGB Response

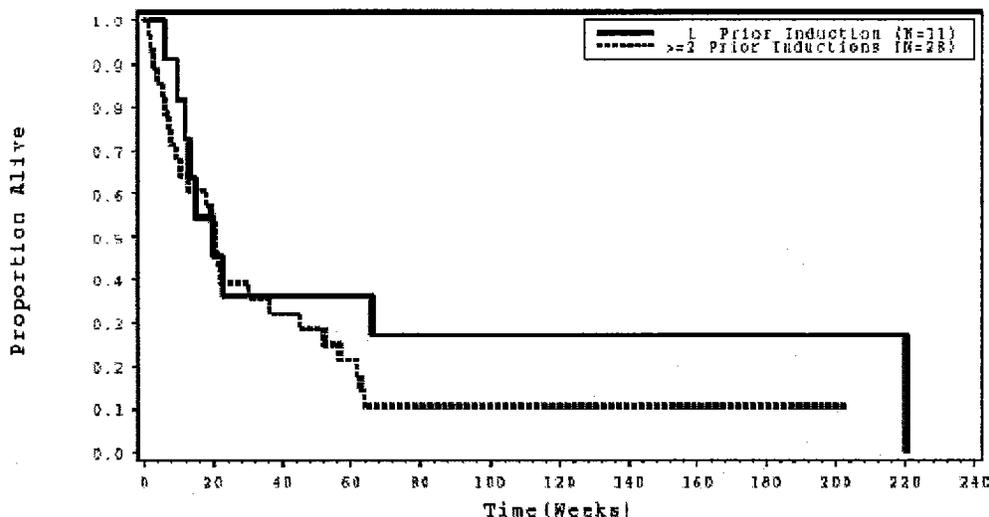
Number of prior Inductions	Subject	Time to CALGB CR (Weeks)	Time to GSK mCR (Weeks)	Time to GSK CR* (Weeks)	Time to GSK CR (Weeks)
1 Prior Induction	77661	3.1	3.1	5.3	8.3
	82761	6.3	n/a	8.7	11.1
	76579	3.4	3.4	n/a	n/a
	84144	3.1	3.1	3.1	n/a
≥2 Prior Inductions	77798	4.0 ^a	11.7 ^a	11.7 ^a	11.7 ^a
	83908	2.9	2.9	2.9	2.9
	82137	3.1	n/a	3.1	3.9
	79729	3.4	n/a	3.1	3.1
	78326	7.6	n/a	7.6	7.6
	82970	2.7	3.1	n/a	n/a
	76143	3.9	3.9	3.9	n/a
	73718	n/a	3.1	n/a	n/a

Survival

The median survival for all treated subjects with 1 prior induction was 20.1 weeks with a 95% CI of 12.0 to 220 weeks. For all treated subjects with ≥2 prior inductions, the median survival was 20.6 weeks with a 95% CI of 10.4 to 36.4 weeks. Eighteen percent of subjects who received 1 prior induction were censored and 11% of subjects who received ≥2 prior inductions were

censored. The survival curves for the two prior induction groups appear similar as shown in Figure 3.

Figure 3 PGAA 2002: Summary of Overall Survival by Number of Prior Inductions (All Treated Patients) [Sponsor's Analysis]



3.1.2.5 Sponsor's Efficacy Conclusions

- The sponsor believes the response rate observed provides evidence of clinical efficacy based on the protocol specified test of the null hypothesis of a CR probability of $\leq 10\%$ versus an alternative hypothesis consisting of a CR probability of $\geq 30\%$.
- Eleven of the 39 treated subjects (28%) experienced a CALGB complete response to nelarabine during the study period, and 5 subjects (13%) experienced a partial response.
- Four subjects (36%) with 1 prior induction experienced a CALGB complete response as did 7 subjects (25%) with ≥ 2 prior inductions.
- Two subjects (18%) with 1 prior induction experienced a GSK complete response as did 5 subjects (18%) with ≥ 2 prior inductions. All GSK CRs were confirmed 1 month later.
- Nine subjects had a complete response with no evidence of disease with or without hematologic recovery (CR*). Of the 9, seven subjects went on to achieve a complete response with full hematologic recovery (CR) and two had a best response of CR*.
- The range (minimum to maximum) for duration of GSK CR was 15.1 to 212.0 weeks. The range for duration of GSK CR* was 4 to 215 weeks.
- A total of 31% (8/26) of subjects with $\geq 25\%$ blasts at baseline had a mCR. Five of the 17

(29%) eligible subjects with ≥ 2 prior inductions had a mCR.

- The median survival was 20.1 weeks for subjects with 1 prior induction and 20.6 weeks for subjects with ≥ 2 prior inductions.
- The one year survival rate for all treated subjects was 31% with a 95% CI of 16% to 45%. Of the subjects whose disease failed their most recent prior induction, 6 subjects (32%) were alive at one year.
- Of the subjects with ≥ 2 prior inductions whose disease failed to respond to their most recent induction attempt, a complete response was achieved in 18% (3/17) after receiving nelarabine. The duration of response for these three subjects was 15.1, 29.4 and 156.3+ weeks.
- The overall survival was 56.6 and 62.6 weeks for two of the subjects with CRs whose disease had failed to respond to their most recent prior induction. The third subject who achieved a CR was still alive at the date of last contact. This subject's survival was censored at 159.3 weeks.

3.1.2.6 Reviewer's Results

This trial was designed with two stages. If 3 of the first 18 patients achieved responses then the study would accrue an additional 17 patients; otherwise, the trial would be stopped and the drug considered inactive. Six of the first 18 patients achieved CRs and one other attained a CR*. Thus, the study met the protocol specified stage 1 efficacy criteria and was continued into the second stage.

Table 21 shows the CR and CR* overall response rates by the number of prior inductions.

Table 21 PGAA 2002: CRs and CR*s by Number of Prior Inductions (FDA Reviewer's Analyses)

	1 PRIOR INDUCTION N=11	≥ 2 PRIOR INDUCTIONS N=28	ALL N=39
CR	2 (18) [2, 52]	5 (18) [6, 37]	7 (18) [8, 34]
CR*	1 (9) [0, 41]	1 (4) [0, 18]	2 (5) [0, 17]
CR+CR*	3 (27) [6, 61]	6 (21) [8, 41]	9 (23) [11, 39]

Time to complete response ranged from 2.9 to 11.7 weeks and time to CR* ranged from 2.9 to 11.7 weeks.

Two of the three patients who attained CR or CR* in the group with 1 prior induction had stem cell transplants after nelarabine therapy. Two of the six patients that attained CR or CR* in the group with 2 or more prior inductions had stem cell transplants after nelarabine therapy. The effect of Nelarabine on the duration of response is therefore confounded with the effect of the

stem cell transplant for these patients. Table 22 shows the duration of the best response for patients with CR or CR* who did not receive stem cell transplants.

Table 22 PGAA 2002: Durations of CR or CR* for non-transplanted patients (FDA Reviewer's results)

1 Prior Induction		≥ 2 Prior Inductions	
Subject ID	Duration	Subject ID	Duration
77661	212	78326	195.4+
		82137	29.4
		77798	18.9
		76143	4.0

Because this was an open label, non-randomized, uncontrolled study no statistical comparisons could be made. Therefore, clinical judgment is needed to evaluate the efficacy of Nelarabine.

3.2 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review(s) for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

This section contains this reviewer's summary statistics for gender, race, and age subgroups. The studies were not adequately powered to estimate response rates in subgroups precisely or to detect differences between subgroups.

Gender

In PGAA 2001, 70% of stratum 1 and 2 patients were male. Although female CR and CR* rates were slightly higher than male CR and CR* rates in PGAA 2001 (see Table 23), the differences were not statistically significant.

Table 23 PGAA 2001: CR and CR* rates by Gender

STRATUM	GENDER	CR	CR*	CR+CR*	<CR*
1	Male	11 (35.5)	3 (9.7)	14 (45.2)	17 (54.8)
1	Female	3 (50.0)		3 (50.0)	3 (50.0)
2	Male	2 (6.9)	4 (13.8)	6 (20.7)	23 (79.3)
2	Female	4 (21.1)	2 (10.5)	6 (31.6)	13 (68.4)
1 & 2	Male	13 (21.7)	7 (11.7)	20 (33.3)	40 (66.7)
1 & 2	Female	7 (28.0)	2 (8.0)	9 (36.0)	16 (64.0)

In PGAA 2002, 32 out of 39 (82%) patients were male. There were only 2 females in the 1 prior induction group and only 5 females in the group with ≥ 2 prior inductions. Thus, there were not

sufficient numbers to reliably estimate the adult female CR and CR* rates. Nevertheless, the results are shown in Table 24.

Table 24 PGAA 2002: CR and CR* rates by Gender

PRIOR INDUCTIONS	Gender	CR	CR*	CR+CR*	<CR*
1	Male	2 (22.2)	1 (11.1)	3 (33.3)	6 (66.7)
1	Female	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
2	Male	4 (17.4)	0 (0.0)	4 (17.4)	19 (82.6)
2	Female	1 (20.0)	1 (20.0)	2 (40.0)	3 (60.0)
1 or >= 2	Male	6 (18.8)	1 (3.1)	7 (21.9)	25 (78.1)
1 or >= 2	Female	1 (14.3)	1 (14.3)	2 (28.6)	5 (71.4)

Age

Study PGAA 2001 was primarily a pediatric study although it allowed individuals up to 21 years of age to enter. Study PGAA 2002 was an adult study but only two individuals were 65 or older. Therefore, no meaningful analysis of the age >= 65 subgroup is possible.

In PGAA 2001 ages ranged between ½ year and 21 years. The mean age among stratum 1 and 2 patients was 11.3. Table 25 shows the CR and CR* rates for the age < 12 and age ≥ 12 subgroups. There were no consistent differences between the < 12 and ≥ 12 age groups.

Table 25 PGAA 2001: CR and CR* Rates by Age Group

STRATUM	AGE GROUP	CR	CR*	CR+CR*	<CR*
1	< 12	10 (47.6)	2 (9.5)	12 (57.1)	9 (42.9)
1	>=12	4 (25.0)	1 (6.3)	5 (31.3)	11 (68.8)
2	< 12	3 (11.1)	2 (7.4)	5 (18.5)	22 (81.5)
2	>=12	3 (14.3)	4 (19.0)	7 (33.3)	14 (66.7)
1 & 2	< 12	13 (27.1)	4 (8.3)	17 (35.4)	31 (64.6)
1 & 2	>=12	7 (18.9)	5 (13.5)	12 (32.4)	25 (67.6)

In PGAA 2002 ages ranged between 16 and 66. Only two patients were 65 or older. The mean age was 35. Table 26 shows the CR and CR* rates by age group (<35 and ≥ 35). There were no consistent differences between the < 35 and ≥ 35 age groups.

The ages of CR or CR* patients in PGAA 2002 with at least 2 prior inductions were 18, 21, 22, 38, 38, and 39. The ages of CR or CR* patients in PGAA 2002 with 1 prior induction were 23, 25, and 28.

Table 26 PGAA 2002: CR and CR* Rates by Age Group

Prior Inductions	AGE GROUP	CR	CR*	CR+CR*	<CR*
1	< 35	2 (33.3)	1 (16.7)	3 (50.0)	3 (50.0)
1	>=35	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
≥ 2	< 35	2 (12.5)	1 (6.3)	3 (18.8)	13 (81.3)
≥ 2	>=35	3 (25.0)	0 (0.0)	3 (25.0)	9 (75.0)
1 or >= 2	< 35	4 (18.2)	2 (9.1)	6 (27.3)	16 (72.7)

1 or >= 2	>=35	3 (17.6)		3 (17.6)	14 (82.4)
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Race

In stratum one of PGAA 2001 59% were White, 22% were Black, 16% were Hispanic, and 3% were from other races. In stratum two 65% were White, 10% were Black, 17% were Hispanic and 8% were from other races. Table 27 displays the CR and CR* rates by Race.

Table 27 PGAA 2001: CR and CR* Rates by Race

STRATUM	RACE	CR	CR*	CR+CR*	<CR*
1	white	9 (40.9)	3 (13.6)	12 (54.5)	10 (45.5)
1	Hispanic	1 (16.7)	0 (0.0)	1 (16.7)	5 (83.3)
1	Black	4 (50.0)	0 (0.0)	4 (50.0)	4 (50.0)
1	other	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
2	white	4 (12.9)	4 (12.9)	8 (25.8)	23 (74.2)
2	Hispanic	1 (12.5)	0 (0.0)	1 (12.5)	7 (87.5)
2	Black	0 (0.0)	1 (20.0)	1 (20.0)	4 (80.0)
2	other	1 (25.0)	1 (25.0)	2 (50.0)	2 (50.0)
1 & 2	white	13 (24.5)	7 (13.2)	20 (37.7)	33 (62.3)
1 & 2	Hispanic	2 (14.3)	0 (0.0)	2 (14.3)	12 (85.7)
1 & 2	Black	4 (30.8)	1 (7.7)	5 (38.5)	8 (61.5)
1 & 2	other	1 (20.0)	1 (20.0)	2 (40.0)	3 (60.0)

In study PGAA2002 there were 27 (69.2%) Whites, 9 (23.1%) Blacks, and 1 (2.6%) Asian, 1 (2.6%) Hispanic, and 1 (2.6%) Native American. In the group with 2 or more prior inductions the CR and CR+CR* rates were similar between whites and blacks. There were only 2 patients from other races so there was insufficient data to make any comparisons with other races. Likewise, in the group with only 1 prior induction there was only one non-white patient, so no comparisons of CR rates between races could be made.

Table 28 PGAA 2002: CR and CR* Rates by Race

Prior Inductions	RACE	CR	CR*	CR+CR*	<CR*
1	white	2 (20.0)	1 (10.0)	3 (30.0)	7 (70.0)
1	other	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
≥ 2	white	3 (17.6)	0 (0.0)	3 (17.6)	14 (82.4)
≥ 2	Black	1 (11.1)	1 (11.1)	2 (22.2)	7 (77.8)
≥ 2	other	1 (50.0)	0 (0.0)	1 (50.0)	1 (50.0)
1 or ≥ 2	white	5 (18.5)	1 (3.7)	6 (22.2)	21 (77.8)
1 or ≥ 2	Black	1 (11.1)	1 (11.1)	2 (22.2)	7 (77.8)
1 or ≥ 2	other	1 (33.3)	0 (0.0)	1 (33.3)	2 (66.7)

4.2 Other Special/Subgroup Populations

4.2.1 Response Rates for Individual Investigators

A few PGAA 2001 investigators had response rates that were considerably higher than the average:

In center 1863 2/2 patients had CRs (in stratum 1 2/2 had CRs).

In center 3001 2/3 patients had CRs (in stratum 1 2/2 had CRs).

In center 1897 2/6 patients had CRs and 1/6 had CR*. Of the 3 patients in stratum 1, 2 had CRs and 1 had a CR*.

No investigator in PGAA 2002 had more than one patient with a CR or CR*.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The two phase II studies submitted to support this application were open label, uncontrolled, and non-randomized so no valid statistical comparisons could be made. The sponsor is seeking an indication for T-ALL and T-LBL patients with at least two prior inductions. In the COG (pediatric and adolescent) study the originally planned dose was 1200 mg/m² but this was reduced first to 900 mg/m² and then to 600 mg/m² because of neurotoxicity. The majority of patients were dosed at 650 mg/m² and this is the dose sought in the indication. Complete responses were observed in 5 of 39 (13% [4%, 27%]) patients in the 2 or more prior inductions subgroup who were treated with the 650 dose. An additional 4 patients in this group achieved CR*s (CR w/out hematologic recovery). So a total of 9 of the 39 (23% [11%, 39%]) patients achieved a CR* or better. In the adult study, in which the dose was 1500 mg/m², 5 out of 28 (18% [6%, 37%]) achieved a CR and 1 achieved a CR* for a total of 6 out of 28 (21% [8%, 41%]) with a CR* or CR. Clinical judgment is needed to make a recommendation on efficacy since there was no control group to compare these rates to.

In many cases patients received bone marrow transplants or other systemic or intrathecal therapies after Nelarabine treatment and before disease progression. In such cases the observed durations of complete response may be overestimates of the duration of response due to Nelarabine alone.

5.2 Conclusions and Recommendations

Since the studies submitted to support this application were open label, uncontrolled, and non-randomized no valid statistical comparisons could be made. Clinical judgment is needed to assess the efficacy of this drug.

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