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ORIGINAL ARTICLE

Results of Cancer and Leukemia Group B 10102 (Alliance), a Phase 1/2 Study

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Abstract

Background: Acute lymphoblastic leukemia (ALL) in adults is aggressive, with long-term outcomes impacted by treatment resistance and toxicity. CD52 is expressed in most cases of B- and T-lineage ALL. Alemtuzumab, a humanized immunoglobulin G1 monoclonal antibody that targets CD52, was identified as a potential agent to improve treatment efficacy without increasing toxicity.

Methods: In this phase 1/2 study (Cancer and Leukemia Group B [CALGB] 10102, NCT00061945), a course of single-agent alemtuzumab was intercalated into CALGB

The Clinicaltrials.gov trial identifier is NCT00061945.

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19802 backbone chemotherapy after the third course of intensive chemotherapy in those who were CD52+ at diagnosis. Phase 1 tested three dose levels of subcutaneous alemtuzumab (10, 20, and 30 mg 3 times weekly for 4 weeks/12 doses) and demonstrated that 30 mg was tolerable. Phase 2 established feasibility.

Results: The study enrolled 295 evaluable patients (115 in phase 1, 180 in phase 2); 206 (69.8%) were CD52+. Among evaluable CD52+ patients, 43.7% (90/206) completed the first three treatment modules; 97.8% (88 of 90) were treated with alemtuzumab. Alemtuzumab was associated with cytomegalovirus viremia, which occurred in 23.3% (14 of 60) of patients during and 29.2% (19 of 65) after alemtuzumab treatment. With a median follow-up of 101.2 months, median overall survival (OS) was 26.3 months (3-year rate, 44%; 5-year rate, 36%; 10-year rate, 31%). Landmark analysis at the start of the fourth course of treatment demonstrated no difference in OS or disease-free survival between patients who did and who did not receive alemtuzumab.

Conclusion: Alemtuzumab was feasible to administer in adults with ALL receiving intensive chemotherapy, but was without evidence of benefit.

KEYWORDS
alemtuzumab, ALL, antibody, chemotherapy, monoclonal, older

INTRODUCTION

Acute lymphoblastic leukemia (ALL) in adults is an aggressive hematologic malignancy. In the 1980s and 1990s, the Cancer and Leukemia Group B (CALGB) conducted a series of clinical trials for adults with ALL with the intent of improving outcomes by escalating the intensity of cytotoxic chemotherapy during the early treatment phases, and by increasing the use of nonmyelosuppressive drugs (vincristine, L-asparaginase) during consolidation.[1–6] These strategies were derived from the successful approaches developed for children with high-risk ALL.[7] CALGB is now part of the Alliance for Clinical Trials in Oncology.

Treatment intensification in adults, however, was limited by toxicity, prompting efforts to mitigate therapy-related morbidity and mortality by incorporating age-based chemotherapy dose adjustments and adding filgrastim (G-CSF) prophylaxis to induction.[3–6] Despite these efforts, survival remained poor with long-term remissions achieved by only 30%–50% of patients, depending on age. Similar results were seen in studies of chemotherapy for adult ALL conducted by other groups.[8] Thus, it was recognized that refinement of conventional chemotherapy approaches had limited ability to further improve outcomes. Instead, novel treatment modalities would be needed. Monoclonal antibodies were recognized as a promising therapeutic strategy for treating ALL, inspired by the successful incorporation of rituximab into chemotherapy regimens for adults with lymphoma.[9]

Alemtuzumab, a humanized immunoglobulin G1 monoclonal antibody that targets CD52, was a promising candidate treatment because CD52 is expressed on lymphocytes, including lymphoblasts, but not on normal hematopoietic cells.[10] Additionally, CD52 was believed to be a good target for antibody-induced complement-mediated lysis and antibody-dependent cellular toxicity.[11,12] Experience with alemtuzumab in ALL before this study was limited, but alemtuzumab was being developed in chronic lymphocytic leukemia (CLL), supporting a study of alemtuzumab in adult ALL.[13–17] The hypothesis was that alemtuzumab might eliminate minimal residual disease (MRD) persisting after initial chemotherapy and thereby improve disease-free survival (DFS). Given profound lymphocyte depletion induced by alemtuzumab, infectious complications including cytomegalovirus (CMV) viremia were a concern.

The phase 1/2 CALGB 10102 study (NCT00061945) was designed to test the safety and preliminary efficacy of adding alemtuzumab to ALL chemotherapy in adults with CD52-expressing ALL.[6] A 4-week module of single-agent alemtuzumab was intercalated into the backbone chemotherapy tested in CALGB 19802, approximately 3 months after study entry, at a time when patients were anticipated to be in a stable hematologic remission. This report describes the long-term outcomes of all treated patients.

MATERIALS AND METHODS

Eligibility and study entry

Patients ≥15 years old with untreated precursor B-cell or T-cell ALL were eligible. There were no absolute exclusions for organ function, although the potential for increased toxicity due to the presence of a psychiatric or medical comorbidity was considered.

Samples from each patient were submitted for central morphology review, cytogenetic analysis, and immunophenotyping including CD52 expression. Patients with ≥10% CD52 expression on lymphoblasts were considered CD52-positive. A high white blood cell (WBC) count was defined as WBC >30,000/μL (B-lineage) or >100,000/μL (T-lineage). High cytogenetic risk was defined as t(9;22)(q34;q11.2), t(4;11)(q21;q23) or other balanced translocations involving band 11q23, chromosome 7 loss, chromosome 8 gain, and hypodiploidy with a chromosome number ≤43.

Each participant signed an institutional review board-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines. All patients were registered at the time of initial entry, and then again after three courses of therapy as outlined below.

Treatment overview

CALGB 10102 treatment included six modules of intensive therapy (A1, B1, C1, A2, B2, and C2) followed by maintenance therapy until 24 months from study entry (Figure 1). Eligible patients received 4 weeks of alemtuzumab (module D) after C1. Treatment was modified during module A for patients aged ≥60 years. Allogeneic transplant was recommended for patients with t(4;11) at the earliest possible time if a matched donor was available.

If the Philadelphia (Ph)-chromosome [i.e., t(9;22)(q34;q11.2); abbreviated Ph hereafter] was identified, imatinib 400 mg daily was added on day 15 of module A1 and continued at this dose except during alemtuzumab treatment and was increased to 600 mg daily during maintenance. Patients aged <60 years with Ph + ALL were removed from study after achievement of first complete remission (CR1) and enrolled in CALGB 10001.[18]

The protocol recommended antibacterial and antifungal prophylaxis during neutropenia and prophylaxis for *pneumocystis jirovecii* beginning during B1. Granulocyte-colony stimulating factor (G-CSF) was recommended during A and B modules.[4] Antiviral therapy with acyclovir or valacyclovir was required during the alemtuzumab treatment module and for 6 months afterward.

Study intervention: alemtuzumab (module D)

Patients were eligible to receive alemtuzumab (module D) if the following parameters were met: achieved complete remission (CR) with absolute neutrophil count (ANC) ≥1500/μL and platelet count >100,000/μL, AST less than three times upper limit of normal (ULN), CMV negative by polymerase chain reaction (PCR), and absence of serious infection. Alemtuzumab was supplied by the National Cancer Institute (NCI) and was administered as a subcutaneous injection three times per week on an alternate day schedule for 4 weeks (12 total doses). During the first week of therapy, patients received the first dose of alemtuzumab at 3 mg, the second dose at 10 mg, and subsequent doses per cohort assignment. In phase 1, patients were assigned to receive alemtuzumab at assigned dose level: cohort 1, alemtuzumab at 10 mg subcutaneously three times per week; cohort 2, alemtuzumab at 20 mg subcutaneously three times per week; and cohort 3, alemtuzumab at 30 mg SC three times per week. In phase 2, patients received alemtuzumab at 30 mg subcutaneously three times per week, the recommended phase 2 dose determined in phase 1.

During alemtuzumab treatment, patients received acyclovir 800 mg four times daily or valacyclovir 2 g four times daily, which was continued for 6 months after completion of alemtuzumab therapy and recovery of CD4 and CD8 counts to the normal range. Monitoring for CMV infection with CMV DNA PCR assay was conducted weekly during treatment and then every 2 weeks for 2 months following completion of alemtuzumab. Alemtuzumab was discontinued for CMV viremia or CMV disease, and the patient was treated with intravenous ganciclovir.

Study assays

Measurable residual disease (MRD) was assessed using clone-specific quantitative PCR (sensitivity of 10^{-4} to 10^{-5}) of immunoglobulin H or T-cell receptor clonal rearrangements, as previously described. MRD was assessed at time points after completion of modules A1, C1, and D (alemtuzumab).[19] Analysis of CD52 expression described in the Supporting Methods.

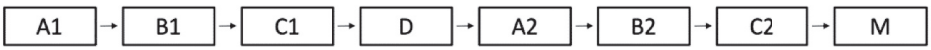
Statistical methods

The primary objective of the phase 1 study was to determine the maximum tolerated dose (MTD) of alemtuzumab during post remission treatment. At least six patients (and nor more than 12) were enrolled for safety/tolerability to each of the 3 dose levels (113, 213 and 313 mg, respectively). The MTD was the highest alemtuzumab dose (not to exceed 30 mg) at which <40% of patients developed a dose-limiting toxicity (DLT) with a DLT defined as inability to proceed to next protocol treatment (i.e., module A2) due to medical complication (infection, cytopenias, or other) within 6 weeks of the last dose of alemtuzumab.

The primary objective of the phase 2 study was to ensure that at least 80% of patients entering alemtuzumab treatment (module D) could continue protocol treatment (module A2) within 6 weeks of the last dose of alemtuzumab. A planned sample size of 35 patients who started alemtuzumab (module D) would yield a power of 84% and a type I error rate of 0.08 to detect a 80% feasibility rate against 60%. Secondary objectives included determining the toxicity profile of alemtuzumab, determining the ability of alemtuzumab to modulate MRD and outcomes, and correlating outcomes with pretreatment characteristics.

Accrual was planned to exceed sample size of evaluable patients able to proceed with module D (alemtuzumab). This was necessary to account for lack of CD52 positivity, removal of Ph+ patients for

Schema



Module A (28 days)
Cyclophosphamide 1000 mg/m^2 intravenous (IV) day 1 (*omit if ≥60 years*)
Daunorubicin 80 mg/m^2 days 1-3 (*if ≥60 years, 60 mg/m^2*)
Dexamethasone 5 mg/m^2 oral (PO) twice daily days 1-7, 15-21 (day 1-7 only in A2)
Vincristine 2 mg IV days 1, 8, 15, 22
L-asparaginase 6000 U/m^2 subcutaneous (SC)/intra-muscular (IM) days 5, 8, 11, 15, 18, 22
Imatinib 400 mg/day from day 15 onward, if Philadelphia chromosome (Ph) positive*
G-CSF (filgrastim) 5 μg/kg/day from day 4 onward

Module B (28 days)
Cytarabine 2000 mg/m^2 IV days 1-3
Cyclophosphamide 1000 mg/m^2 IV day 1
L-asparaginase 6000 U/m^2 days 15, 18, 22
G-CSF (filgrastim) 5 μg/m^2 SC day 4 until ANC >5000/μl
Intrathecal (IT) methotrexate (MTX) 15 mg Day 1
Imatinib 400 mg/day PO daily, if Ph-positive

Module C (42 days)
Vincristine 2 mg days 1, 8, 15
MTX IV 1000 mg/m^2 IV over 3 hours days 1, 15, 29
MTX PO 25 mg/m^2 every 6 hours beginning 6 hours after initiation of IV on days 1, 15, 29
Leucovorin 25 mg/m^2 IV 6 hours after last dose of MTX oral on days 2, 16, 30
Leucovorin 10 mg oral every 6 hours for 8 doses and/or until MTX level <0.05 μM
6-mercaptopurine (6-MP) 60 mg/m^2 PO days 1-35
MTX 15 mg IT days 1, 15, 29
Imatinib 400 mg/day PO daily, if Ph-positive

Module D (28 days), if eligibility criteria met (otherwise skip to A2)
Week 1 Ramp UP: initial dose 3 mg; second dose 10 mg; third dose onward per target dose level per cohort assignment as below)
Phase 1
Cohort 1 10 mg SC 3 times per week x 4 weeks (12 total doses)
Cohort 2 20 mg SC 3 times per week x 4 weeks (12 total doses)
Cohort 3 30 mg SC 3 times per week x 4 weeks (12 total doses)
Phase 2
Cohort 3 30 mg SC 3 times per week x 4 weeks (12 total doses)
G-CSF (filgrastim) as needed; NO imatinib

Module M (POMP Maintenance) – 4 week cycles until 24 months from date of study entry
6-MP 60 mg/m^2 PO daily
Vincristine 2 mg day 1
Dexamethasone 6 mg/m^2 oral days 1-5
MTX 20 mg/m^2 PO day 1
Imatinib 600 mg/day PO daily, if Ph-positive

FIGURE 1 CALGB 10102 chemotherapy schema. Patients ≤60 years found to be Philadelphia (Ph) chromosome–positive, were removed from study and enrolled on CALGB 10001 after achievement of complete remission. CALGB indicates Cancer and Leukemia Group B.

alternative treatment, and patient attrition before module D. Thus, the total number of initially registered patients planned for this entire study was approximately 272–300.

A complete remission (CR) was defined as <5% blasts with marrow cellularity >20%, resolution of extramedullary manifestations of disease, ANC >1500/μL, and platelets >100,000/μL. Overall

survival (OS) was defined as time from study registration until death or last contact. Disease-free survival (DFS) was defined as time from achievement of CR until death, relapse, or last clinical assessment. OS and DFS were estimated using the Kaplan–Meier method with confidence intervals. A univariate Cox proportional hazards model was evaluated for each parameter (age, sex, cytogenetics, lineage, and WBC). Parameters with a p value <.15 in the univariate models were brought forward to the multivariate Cox proportional hazards model analysis using backward variable selection methods. All analyses were done in SAS 9.4. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Management Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. The progress of the study was monitored via regularly scheduled conference calls involving the study chair, statisticians and data coordinator. Submission of induction toxicity forms to the study chair from treating institutions was mandatory at weekly intervals during the phase 1 portions. All analyses were based on the study database frozen on September 19, 2016.

RESULTS

Patients

Between September 2003 and April 2007, 302 patients were registered on CALGB 10102 from 30 member institutions. Among registered patients, two were cancelled and five were ineligible, yielding 295 evaluable patients with 115 patients enrolled in phase 1 and 180 patients enrolled in phase 2 (Figure 2). Patient characteristics are listed in Table 1. Twenty-three percent were ≥60 years old and 43% were women. Race was 83% White (246 of 295), 9% Black (28 of 295), 3% Asian (nine of 295), <1% Native American (one of 295), and 4% (11 of 295) unknown or not reported. Eighty-two percent were B-lineage, 16% were T-lineage; 20% had Ph+ ALL and 7.5% had t(4;11). Among the 295 evaluable patients, 59.7% (176 of 295) were CD52+ and B-cell, 22.0% (65 of 295) were CD52− and B-cell, 9.2% (27 of 295) were CD52+ and T-cell, 6.4% (19 of 295) were CD52− and T-cell, 1.0% (three of 295) were CD52+ and missing lineage, and 1.7% (five of 295) were CD52− and missing lineage.

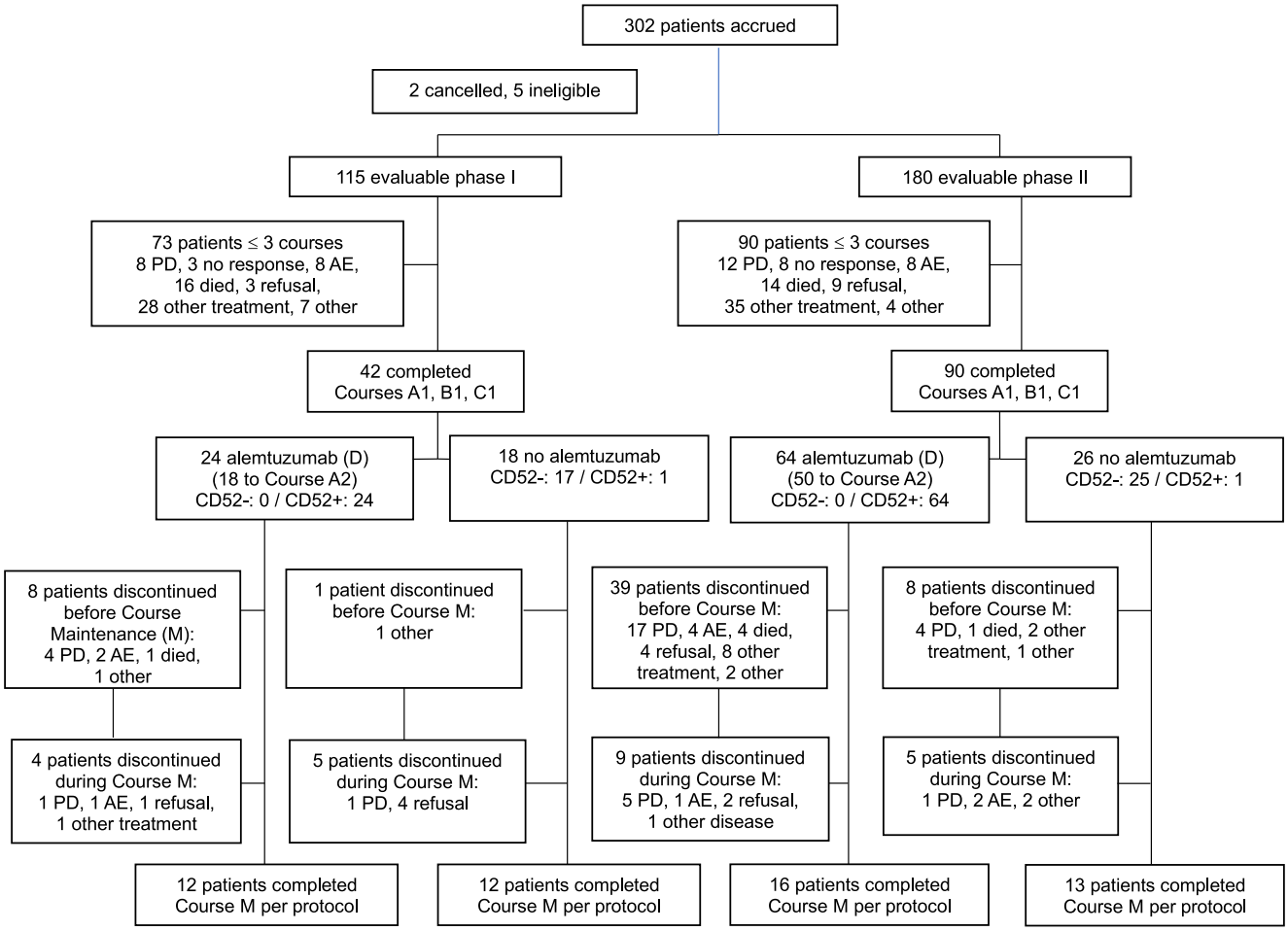


FIGURE 2 Consolidated Standards of Reporting Trials diagram. AE indicates adverse event; PD, progressive disease.

TABLE 1 Patient characteristics (n = 295).

Characteristic	No. (%)
Age (years), median (range)	47.0 (17.4–79.8)
Age category (years)	
17–39	117 (40)
40–49	44 (15)
50–59	67 (23)
60–80	67 (23)
Sex	
Male	168 (57)
Female	127 (43)
Race	
American Indian or Alaska Native	1 (<1)
Asian	9 (3)
Black	28 (9)
White	246 (83)
Unknown/unreported	11 (4)
Immunophenotype	
B-cell	241 (82)
CD52+	176 (73)
CD52−	65 (27)
T-cell	46 (16)
CD52+	27 (59)
CD52−	19 (41)
Unknown	8 (3)
CD52+	3 (37.5)
CD52−	5 (62.5)
WBC	
B-cell, <30,000/μL	166 (56.3)
B-cell, ≥30,000/μL	64 (21.7)
T-cell, <100,000 K/μL	36 (12.2)
T-cell, ≥100,000 K/μL	6 (2.0)
Missing/not reported	23 (7.8)
Karyotype	
Favorable	16 (5.4)
Intermediate	70 (23.6)
Philadelphia chromosome–positive (Ph+)	59 (19.9)
Unfavorable (excluding Ph+)	56 (18.9)
t(4;11)	22 (7.5)
Not classified/missing	94 (31.8)

Abbreviation: WBC, white blood cell.

Treatment and response

Among 295 evaluable patients, only 18.0% (53 of 295) completed planned protocol therapy. Reasons for not completing protocol therapy included pursuit of other therapy including stem cell transplantation in 25.1% (74 of 295) of patients, no response to or progressive disease on treatment in 21.7% (64 of 295), death on treatment in 12.2% (36 of 295), toxicity during treatment in 8.8% (26 of 295), patient refusal in 7.8% (23 of 295), other reasons in 6.1% (18 of 295), and development of another disease in 0.3% (one of 295), as outlined in the Consolidated Standards of Reporting Trials diagram (Figure 2). A total of 50 patients underwent transplant, the majority in CR1 (only eight had prior progression or relapse).

A CR was achieved in 79.7% of evaluable patients (235 of 295, 95% confidence interval [CI] 74.6%–84.1%) with 91% of remissions achieved after the initial treatment module (A1, Table 2). Younger patients (17–39 years old) more frequently achieved CR (86.3%, 101 of 117) compared with older patients (40–59 years old: 78.4%, 87 of 111; ≥60 years old: 70.1%, 47 of 67; p = .029). Early mortality within 60 days was 11.5% overall, and more frequent in older patients (17–39 years old: 3.4%, four of 117; 40–59 years old: 11.7%, 13 of 111; ≥60 years old: 25.4%, 17 of 67; p < .001).

With a median follow-up of 101.2 months (range: 3.5–128.9), 67.1% (198 of 295) of patients were known to have died, whereas remaining patients were known alive at last follow-up (32.9%, 97 of 295). Median OS was 26.3 months (95% CI, 20.3–35.4) with 3-year, 5-year, and 10-year OS rates estimated at 44% (95% CI, 0.38%–0.50%), 36% (95% CI, 0.31%–0.42%), and 31% (95% CI, 0.26%–0.37%), respectively (Table 2; Figure 3).

Among those who achieved CR (n = 235), 35.3% (83 of 235) relapsed with median time to relapse of 7.9 months (range: 0.26–40.4 months), with 59.0% (49 of 83) of relapses occurring within 1 year and 86.7% (72 of 83) within 2 years. There were very few late relapses, with 96.4% (80 of 83) occurring within 3 years and only three relapses occurring between 3 and 5 years of achieving CR. Among patients who relapsed, 5.4% (16 of 295) experienced a central nervous system relapse (three with concurrent and one with prior marrow relapse). Median DFS was 24.8 months (95% CI, 19.1–37.1), with 3-year, 5-year, and 10-year DFS rates estimated at 44.1% (95% CI, 37.6%–50.4%), 36.9% (95% CI, 30.6%–43.2%), and 27.6% (95% CI, 20.5%–35.1%), respectively (Table 2; Figure 3).

In unadjusted analyses, OS and DFS were superior in younger patients and among patients with low WBC count at study entry (Figure 3; Figure S1). There were no differences in OS or DFS by lineage (B vs. T) or cytogenetic risk (Figure S1).

Among 33 patients with MRD assessed at CR after module A1 (approximately day 29) via clone-specific quantitative PCR, DFS was superior in patients who were MRD-negative (n = 29, events n = 16; median DFS, 29.8 months [95% CI, 8.9–Not estimated]) compared to MRD-positive (n = 4, events n = 4; median DFS, 6.4 months [95% CI,

TABLE 2 Outcomes (CR, early mortality, DFS, and OS), overall and by age group and cell lineage.

	CR (%)	Early mortality (within 60 days) (%)	Time	DFS	OS
Overall	79.7	11.5	3-year	0.44 (95% CI, 0.38–0.50)	0.44 (95% CI, 0.38–0.50)
			5-year	0.37 (95% CI, 0.31–0.43)	0.36 (95% CI, 0.31–0.42)
			10-year	0.28 (95% CI, 0.21–0.35)	0.31 (95% CI, 0.26–0.37)
Age (years)			3-year		
17–39	86.3	3.4		0.54 (95% CI, 0.44–0.63)	0.61 (95% CI, 0.52–0.69)
40–59	78.4	11.7		0.44 (95% CI, 0.34–0.55)	0.39 (95% CI, 0.30–0.48)
≥60	70.1	25.4		0.23 (95% CI, 0.13–0.36)	0.22 (95% CI, 0.13–0.33)
			5-year	0.49 (95% CI, 0.39–0.59)	0.52 (95% CI, 0.43–0.61)
				0.34 (95% CI, 0.24–0.44)	0.35 (95% CI, 0.26–0.43)
				0.17 (95% CI, 0.08–0.29)	0.12 (95% CI, 0.0.5–0.24)
			10-year	0.43 (95% CI, 0.32–0.53)	0.47 (95% CI, 0.38–0.56)
				0.23 (95% CI, 0.13–0.36)	0.30 (95% CI, 0.21–0.38)
				NE (95% CI, NE–NE)	NE (95% CI, NE–NE)
Lineage			3-year		
B-cell and Ph+	74.1	15.5		0.37 (95% CI, 0.23–0.52)	0.38 (95% CI, 0.25–0.50)
B-cell and Ph–	78.7	13.1		0.49 (95% CI, 0.41–0.57)	0.48 (95% CI, 0.40–0.55)
T-cell	91.3	0.0		0.37 (95% CI, 0.23–0.52)	0.43 (95% CI, 0.28–0.57)
Unknown	75.0	12.5		0.17 (95% CI, 0.008–0.52)	0.13 (95% CI, 0.007–0.42)
			5-year	0.27 (95% CI, 0.15–0.42)	0.29 (95% CI, 0.40–0.55)
				0.42 (95% CI, 0.34–0.50)	0.41 (95% CI, 0.33–0.48)
				0.32 (95% CI, 0.18–0.47)	0.33 (95% CI, 0.20–0.47)
				0.17 (95% CI, 0.008–0.52)	0.13 (95% CI, 0.007–0.42)
			10-year	0.18 (95% CI, 0.07–0.32)	0.21 (95% CI, 0.12–0.33)
				0.30 (95% CI, 0.21–0.41)	0.36 (95% CI, 0.28–0.43)
				0.32 (95% CI, 0.18–0.47)	0.30 (95% CI, 0.17–0.44)
				NE (95% CI, NE–NE)	NE (95% CI, NE–NE)

Abbreviations: CI, confidence interval; CR, complete remission; DFS, disease-free survival; NE, not estimated; OS, overall survival.

4.2–22.0], $p = .011$) (Figure S2). Among 31 patients with MRD assessed after the third module (C1), there was no significant difference in DFS between those who were MRD-negative ($n = 26$) versus MRD-positive ($n = 5$).

Univariate analysis revealed that sex, WBC, and age were associated with OS with a p value <.15 (0.15 threshold was used given the exploratory nature of this analysis); age and WBC retained significance in the final multivariable model (Table 3). Similar results were obtained for DFS.

CD52 expression

To determine whether CD52 antigen expression correlated with immunophenotype and specific molecular genetic subsets of adult ALL, antibody bound per cell (ABC) was assessed in a randomly selected subset of 88 untreated patients (72 [81%] B-cell ALL, 16 [19%] T-cell ALL) (Table 4). The median ABC for B-cell ALL was 37,178 (range: 1545–228,247), which was significantly higher than the median ABC of 15,585 (range: 5231–53,409) for T-cell ALL cases ($p = .0116$). Interestingly, ABC on both B- and T-lymphoblasts was significantly lower than ABC of residual normal B- and T-lymphocytes ($p < .001$). ABC by cytogenetic subset was also evaluated for commonly recurring abnormalities and differed significantly across the cytogenetic subsets examined ($p < .002$). The highest ABC levels were noted in patients with t(9;22), abnormalities of 9p, and a normal karyotype.

Alemtuzumab

Among the 295 evaluable patients, 206 (69.8%) were CD52+; 43.7% (90/206) of CD52+ patients completed the first three treatment

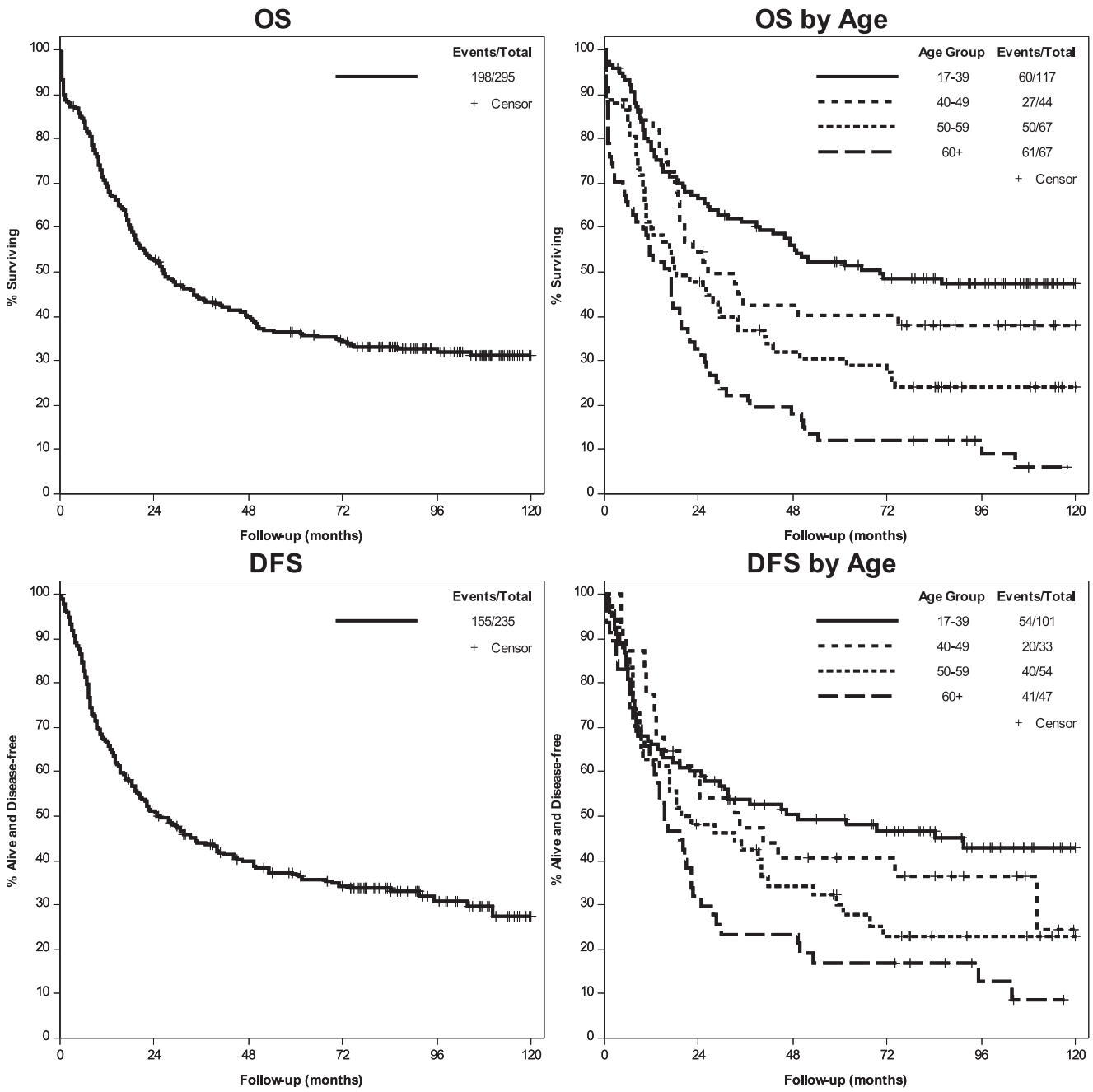


FIGURE 3 Overall survival (overall and by age) and disease-free survival (overall and by age).

modules. Of these 90 patients, 97.8% (88 of 90) received alemtuzumab and 2.2% (two of 90) refused. Overall, 42.7% (88 of 206) of CD52+ patients who initially enrolled received alemtuzumab (24 in phase 1, 64 in phase 2) (Figure 2).

In the phase 1 cohort, one of six (16%) patients in dose level 1 experienced a DLT, three of 10 (30%) patients in dose level 2 experienced a DLT, and two of eight (25%) patients in dose level 3 experienced a DLT. Thus, the maximum tolerated dose was determined to be 30 mg subcutaneously three times per week (Table S1). In the phase 2 cohort, 50 of 64 (78%) of patients were able to continue with protocol treatment. Among the 14 patients who did not continue, 10 did not continue due to relapse and one died during treatment (details unavailable). The remaining three did not continue due to decision to pursue nonprotocol treatment ($n = 1$), refusal ($n = 1$), or other reasons ($n = 1$, no further details available) (Table S1).

Among all 88 patients who received alemtuzumab, the median alemtuzumab dose received was 313 mg (range: 3–403), which varied by cohort. In phase 1 cohort 1, 67% (four of six) of patients received the expected dose of 113 mg (range: 106–120, median 113). In phase 1 cohort 2, 70% (seven of 10) of patients received the expected dose of 213 (range: 3–223, median 213). In phase 1 cohort 3, 100% (eight of eight) of patients received the expected dose of 313 (range: 313–

TABLE 3 Univariate and multivariable model for OS and DFS.

No.	Parameter	Subgroup	*p*	HR (death)	95% HR confidence limits
Univariate analysis for OS					
215	Sex (reference group male)	Female	.0382	1.405	(1.019–1.938)
215	Age, years		<.0001	1.027	(1.017–1.037)
215	Age group	41–60	<.0001	0.500	(0.335–0.747)
	(reference group >60)	≤40		0.316	(0.210–0.475)
215	Cytogenetics (reference group unfavorable/Ph+)	Favorable	.3460	0.657	(0.329–1.310)
		Intermediate		0.649	(0.419–1.004)
		Unclassified		0.818	(0.492–1.361)
		Unfavorable		0.883	(0.565–1.380)
215	Lineage	B	.8321	1.046	(0.693–1.577)
215	WBC	Low risk[a]	.1090	0.760	(0.543–1.063)
33	MRD (reference group: positive)	Negative	.4587	0.624	(0.180–2.171)
Multivariate analysis for OS					
215	Age, years		<.0001	1.029	(1.019–1.039)
215	WBC	Low risk[a]	.0117	0.645	(0.458–0.907)
Univariate analysis for DFS					
171	Sex	Female	.8508	1.036	(0.716–1.499)
171	Age, years		.0015	1.018	(1.007–1.029)
171	Age group	41–60	.0045	0.561	(0.349–0.901)
	(reference group >60)	≤40		0.465	(0.292–0.738)
171	Cytogenetics (reference group unfavorable/Ph+)	Favorable	.7108	0.733	(0.337–1.597)
		Intermediate		0.724	(0.443–1.185)
		Unclassified		0.966	(0.550–1.696)
		Unfavorable		0.857	(0.508–1.446)
171	Lineage	B	.6798	0.911	(0.585–1.418)
171	WBC	Low risk[a]	.0482	0.676	(0.459–0.997)
33	MRD (reference group: positive)	Negative	.0184	0.260	(0.085–0.797)
Multivariate analysis for DFS					
171	Age, years		.0006	1.020	(1.008–1.031)
171	WBC	Low risk[a]	.0144	0.611	(0.412–0.907)

Abbreviations: CI, confidence interval; CR, complete remission; DFS, disease-free survival; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival; WBC white blood cell.

[a]Defined as <30,000/μL for B cell and <100,000/μL for T cell.

313, median 313). Finally, in phase 2, 60.9% (39 of 64) of patients received the expected dose of 313 mg (range: 13–403, median 313), including three patients who were recorded as receiving more than maximum expected dose for unknown reasons.

Two patients who had detectable MRD after the third module (C1) before alemtuzumab (module D) remained MRD-positive after alemtuzumab. Among 19 patients who were MRD-negative, 17 remained negative and two patients became MRD-positive after alemtuzumab. Of 88 patients treated with alemtuzumab, 20 exited the protocol during or at the end of alemtuzumab treatment: 13 for disease progression, two for death on treatment, one for toxicity, and four for refusal/other reasons.

Among 60 of 88 patients with information collected on infectious complications, 23.3% (14 of 60) developed CMV viremia during alemtuzumab treatment. Among 65 of 68 patients with available information after alemtuzumab treatment, 29.2% (19 of 65) later

TABLE 4 ABC medians and ranges by cytogenetic subgroups of interest.

Cytogenetic Subset			ABC on blasts	
Total number of cases studied (n = 45)	***N***	**(%)**	**Median**	**Range**
t(9;22)(q34;q11.2)	14	31	37,558	(11,771–135,085)
t(4;11)(q21;q23) or other translocation involving 11q23	7	14	3826	(1685–4950)
Abnormality involving 9p	7	17	53,166	(3731–206,952)
Normal karyotype	12	24	36,127	(5829–111,443)
–7	2	6	n/a	(42,905–52,452)
Abnormality involving 14q	2	6	n/a	(9967–17,203)
t(1;19)(q23;p13.3)	1	2	n/a	(20,608)

Abbreviations: ABC, antibody bound per cell; n/a, not available.

developed CMV viremia. A summary of all infections occurring during and after alemtuzumab treatment is provided in Tables S2 and S3.

A landmark analysis beginning at the fourth course of treatment (either day 1 of alemtuzumab treatment (module D) or module A2 for those not eligible for or refusing alemtuzumab was conducted among patients treated in the phase 1 cohort 3 and phase 2. There was no difference in OS or DFS between patients who did (n = 69) and who did not (n = 26) receive alemtuzumab.

DISCUSSION

ALL in adults remains a challenging disease to treat effectively. Although outcomes in younger adults have improved with successful application of intensive pediatric chemotherapy regimens, this approach is limited in older patients due to unacceptable toxicity.[8,20–24] Although reductions in doses of conventional chemotherapeutic agents are associated with improvement in toxicity in adults, there is also more disease relapse.[25]

It has been established that achievement of an MRD-negative remission early in the course of treatment is associated with improved disease-free survival.[26–29] Thus, to improve survival, effective and tolerable approaches to eradicate reservoirs of disease without increasing therapy-related mortality are needed. Rituximab was the first monoclonal antibody to improve outcomes in adults with ALL,[30,31] but gains were modest and limited to the minor subgroup of B-ALL cases that express CD20. In contrast, at the time CALGB 10102 was designed, CD52 was identified as a more promising target as it is expressed strongly on both B- and T-lymphoblasts. Thus, interest developed in evaluating alemtuzumab as a potential "MRD eraser" in adults with both ALL lineages. Consistent with prior studies, we found that most patients enrolled on CALGB 10102 had ≥10% CD52 expression on lymphoblasts.[11]

Given that alemtuzumab is associated with profound lymphodepletion and risk of infections, notably CMV, the study incorporated alemtuzumab after achievement of morphologic remission and resolution of neutropenia. This approach was found to be safe, with low rates of serious infection including CMV disease, when combined with careful CMV monitoring, prophylaxis, and treatment protocols. Most patients eligible for alemtuzumab were able to complete assigned treatment and continue to subsequent treatment modules with very few exiting the protocol for death or toxicity (three of 88 treated).

Disappointingly, the survival rate at 5 years of all patients on CALGB 10102 was 36% and patients treated with alemtuzumab did not have improved survival compared with patients who did not receive alemtuzumab. The reasons for this are not certain. Because alemtuzumab leads to profound lymphodepletion (and the CD52 quantitative expression was higher on normal vs. malignant lymphoblasts), it is possible that normal immune surveillance mechanisms for potential MRD eradication were absent and/or that the dose and schedule was not appropriate for specific eradication of lymphoblasts. From our analysis of MRD, alemtuzumab failed to effectively modulate MRD, although this observation is based on only a small number of patients. Another possibility is that alemtuzumab was incorporated into treatment too late to impact MRD and overall outcome: 55% of patients in both cohorts had already withdrawn from protocol therapy before the alemtuzumab module. Thus, patients may have relapsed or moved to alternative therapies before having a chance to benefit.

Since the completion of the CALGB 10102 study, there has been significant progress in the treatment landscape for ALL with the development of two highly effective antibody-targeted agents for B-ALL, blinatumomab and inotuzumab ozogamicin.[32,33] Blinatumomab has now been shown in a randomized trial to improve outcomes when incorporated into post-remission therapy, in a manner similar to alemtuzumab in CALGB 10102.[34] Recent data suggest that frontline incorporation of these newer targeted antibodies with minimal (or no) traditional chemotherapy can result in far better outcomes for older adults with Ph– ALL; longer term follow-up is still needed for these reduced intensity approaches and a randomized comparison is underway within the US cooperative groups (Alliance 042001 NCT05303792).[35,36]

Adults with Ph+ ALL, who were included on CALGB 10102 and allowed to receive imatinib are now treated on separate studies designed specifically for this patient subset with dramatically improved

outcomes with the introduction of more potent ABL1 kinase inhibitors and optimized consolidation approaches. A potentially interesting observation from CALGB 10102 is that patients with Ph+ ALL had the highest overall expression of CD52; thus, for patients with Ph+ ALL who proceed to allogeneic transplantation, the incorporation of alemtuzumab into a reduced intensity conditioning regimen could potentially have disease-modulating activity.[37,38]

Despite the failure to demonstrate a benefit from incorporating of alemtuzumab into post-remission therapy for adult ALL, the long-term follow-up of this cohort of patients offers important insights into treatment and outcomes in adult ALL. We have learned from a number of studies in adult ALL that the minority of adults, for a variety of reasons (treatment resistance, treatment toxicity, and treatment "burnout" due to the long duration of arduous therapy), complete all planned protocol therapy.[6,22] In CALGB 10102, only 43.7% completed the first three treatment modules, and only 18% of patients completed all planned treatment. This supports the mandate for more tolerable, shorter, and more effective treatment strategies, particularly for older adults with ALL. The 10-year follow-up of patients enrolled on CALGB 10102 also provides important information about the pattern of relapse in adult ALL where the majority of relapses occur within 3 years.

In summary, the incorporation of alemtuzumab, in sequence with intensive chemotherapy, into frontline therapy was feasible. However, there was no evidence of benefit, and CMV viremia was frequent. More effective antibody therapies are now being tested in a similar fashion in frontline trials for both younger and older adults with ALL. Although alemtuzumab therapy in this trial did not yield a benefit, it ushered in an era where antibody-based eradication of minimal disease after initial chemotherapy safely lead to superior outcomes for patients with B-ALL.

AUTHOR CONTRIBUTIONS

Marlise R. Luskin: Investigation, writing–review and editing, and writing–original draft. **Jun Yin**: Formal analysis, data curation, and writing–review and editing. **Gerard Lozanski**: Investigation and writing–review and editing. **Emily Curran**: Investigation and writing–review and editing. **Gregory Malnassy**: Investigation and writing–review and editing. **Krzysztof Mrózek**: Investigation and writing–review and editing. **Clara D. Bloomfield**: Investigation. **Spero R. Cataland**: Investigation and writing–review and editing. **Noreen Fulton**: Investigation and writing–review and editing. **Jonathan Kolitz**: Investigation and writing–review and editing. **Betsy Laplant**: Investigation and writing–review and editing. **Oudom Kour**: Formal analysis, data curation, and writing–review and editing. **Bayard L. Powell**: Investigation and writing–review and editing. **Ravi Vij**: Investigation and writing–review and editing. **Eunice S. Wang**: Investigation and writing–review and editing. **David Grinblatt**: Investigation and writing–review and editing. **Richard M. Stone**: Investigation and writing–review and editing. **Geoffrey L. Uy**: Investigation and writing–review and editing. **Richard A. Larson**: Investigation and writing–review and editing. **Wendy Stock**: Investigation, conceptualization, writing–review and editing, and supervision.

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DATA AVAILABILITY STATEMENT

De-identified patient data may be requested from Alliance for Clinical Trials in Oncology via Datasharing@alliancenctn.org if data are not publicly available. A formal review process includes verifying the availability of data, conducting a review of any existing agreements that may have implications for the project, and ensuring that any transfer is in compliance with the IRB. The investigator will be required to sign a data release form before transfer.

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SUPPORTING INFORMATION

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