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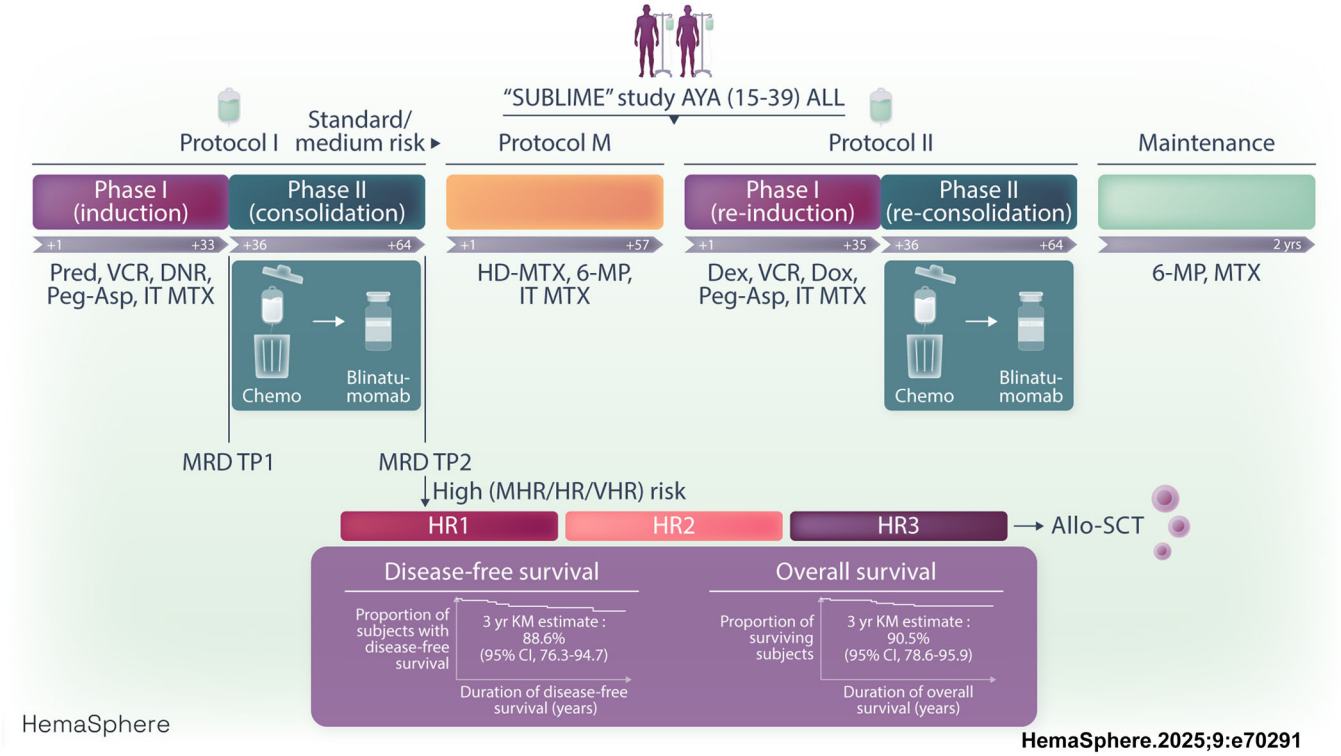
Graphical Abstract



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Abstract

Pediatric regimens improve outcomes in adolescent and young adult (AYA) acute lymphoblastic leukemia (ALL) patients. End-consolidation (time point 2 [TP2]) minimal residual disease negativity (MRD^{neg}) is associated with improved survival. In this study, standard consolidation chemotherapy was replaced with blinatumomab to improve TP2 MRD^{neg}—a key survival surrogate in B-lineage ALL. From 2019 to 2022, 55 patients constituted the intention-to-treat (ITT) cohort, median age 25 (range, 16–39) years. Using a Simon's 2-stage design, blinatumomab replaced standard consolidation chemotherapy cycles with TP2 MRD^{neg} as the primary endpoint. Blinatumomab was associated with an improved TP2 MRD^{neg} rate of 70.8% (95% CI, 55.9%–83.0%) versus the null hypothesis of 60% (P = 0.037). When compared to our previous ALL06 study, median time from protocol I commencement to next treatment phase was 84 versus 97 days (P = 0.0001), with 82.7% versus 45.1% (P < 0.0001), commencing protocol M or high-risk block therapy by day 94. Induction mortality was 1.8%. Blinatumomab was well tolerated. Median follow-up was 42.9 (range, 1.9–54.7) months, with 3-year disease-free survival (DFS) 88.6% (95% CI, 76.3%–94.7%) and 3-year overall survival (OS) 90.5% (95% CI, 78.6%–95.9%) in the ITT cohort. Higher than medium-risk patients had poorer DFS but not OS. Standard genomic risk patients had 100% 3-year DFS and OS. Adverse genomic risk stratified by TP2 MRD^{pos} predicted poorer DFS but not OS. Blinatumomab consolidation for de novo B-lineage AYA ALL was associated with high MRD^{neg} rates and excellent survival, particularly in standard-risk disease. Genomics may assist in predicting response to blinatumomab in de novo ALL (ACTRN12618001734257).

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INTRODUCTION

Pediatric protocols in adolescent and young adult (AYA) acute lymphoblastic leukemia (ALL) patients have improved survival.[1-8] In 2021, the Australasian Leukaemia and Lymphoma Group (ALLG) ALL06 study reported that treatment based on the Australian and New Zealand Children's Haematology and Oncology Group (ANZCHOG) Study 8 was deliverable in an AYA cohort, resulting in 3-year disease-free (DFS) and overall survival (OS) of 72.8% and 74.9%.[8,9] As established by the Associazione Italiana di Ematologia e Oncologia Pediatrica & Berlin-Frankfurt-Münster (AIEOP-BFM) 2000 study, end-consolidation minimal residual disease (MRD) assessed at day 79 (time point 2 [TP2]) was prognostic in ALL06, with TP2 MRD negative (MRD^{neg}) patients having superior DFS and OS.[10] Post hoc genomic analyses demonstrated that adverse risk (AR) genomics were associated with poorer outcomes in ALL06, particularly in association with TP2 MRD positivity (MRD^{pos}).[11] Therapy intensification only partially overcame the inferior prognosis associated with TP2 MRD^{pos}, suggesting that strategies maximizing TP2 MRD^{neg} rates, particularly in AR patients, were key to minimizing relapse and toxicity related to treatment intensification and allogeneic stem cell transplantation (SCT).[8,12]

The bispecific T-cell engager, blinatumomab, has demonstrated efficacy in relapsed/refractory and MRD^{pos} $CD19^{+}$ ALL.[13,14] In the de novo setting, blinatumomab is associated with improved outcomes in infant ALL, in combination with tyrosine kinase inhibitors in Ph+ ALL, or when combined with chemotherapy in children and older ALL patients.[15-21] In the recent LAL2317 study, the addition of two cycles of blinatumomab to the LAL1913 chemotherapy backbone was associated with a 3-year DFS and OS of 70% and 77% in the 18–40 year cohort, respectively, while the addition of four cycles of blinatumomab to standard consolidation in an MRD^{neg} cohort was associated with improved survival in the E1910 study. However, in E1910, only 58.6% of patients proceeded to blinatumomab randomization for reasons including refractory leukemia, relapse, and toxicity.[22,23]

We hypothesized that substituting standard chemotherapy consolidation with a single 28-day cycle of blinatumomab would improve TP2 MRD^{neg} and lead to improved DFS and OS. The primary objective of the ALL09 "SUBLIME—SUbstituting BLinatumomab to Improve MRD Eradication" study was to assess the utility of blinatumomab to improve TP2 MRD^{neg}. In a prespecified retrospective analysis, we also assessed the impact of diagnostic genomics on outcome.

MATERIALS AND METHODS

Patients

From April 2019 through April 2022, 55 patients aged 16–39 years with newly diagnosed precursor B-ALL without t(9;22)/*BCR::ABL1* rearrangement were enrolled to this ALLG cooperative group trial at 15 centers in Australia. Mature-B or Burkitt ALL were excluded. Key inclusion and exclusion criteria are outlined in the ALL09 study protocol provided in the Supporting Information S1. Pregnancy was not an exclusion but required multidisciplinary management plans before study entry. The study received HREC/IRB approval, all participants gave informed consent, and the study was conducted in accordance with the Declaration of Helsinki and registered with the Australasian Clinical Trial Registry (ACTRN12618001734257).

Diagnostic studies

All patients had bone marrow (BM) examination at study entry, with immunophenotyping confirmed by flow cytometry and a diagnosis of CD19+ B-lineage ALL according to the revised World Health Organization (WHO) 2016 criteria.[24] Cytogenetic analyses of BM or peripheral blood (PB) samples were performed locally on all patients, with additional fluorescent in situ hybridization (FISH) studies for *BCR::ABL1* and *KMT2A* rearrangements in patients who failed cytogenetic analyses. Molecular studies for *BCR::ABL1*, *KMT2A::AFF1*, *ETV6::RUNX1*, and *TCF3::PBX1* transcripts were also performed on BM or PB samples at diagnosis. Philadelphia chromosome-positive disease required exclusion by at least two methodologies, including standard karyotype, FISH, or molecular testing.

Complete remission (CR) was defined as no morphological evidence of leukemic cells in PB, with <5% blasts in BM aspirate and no evidence of extramedullary disease. Relapse was defined as the presence of identifiable leukemic cells in PB on blood film, ≥5% blasts in BM aspirate, or recurrence of extramedullary disease.

MRD and genomic testing

MRD testing was performed centrally on BM (Children's Cancer Institute, Sydney) as previously described at day 33 (TP1) post-induction and TP2 post-consolidation, using real-time quantitative-PCR (RQ-PCR) according to EuroMRD criteria.[8,25,26] MRD^{neg} was defined as no detectable specific amplification, and MRD^{pos} was split into low positive (MRD^{lo}), including quantifiable and non-quantifiable positives $<5 \times 10^{-4}$ and high positive (MRD^{hi}) at $\geq 5 \times 10^{-4}$.

Genomic subtyping was performed on all available diagnostic samples ($n = 46$) via whole transcriptomic sequencing and using multiplex ligation-dependent probe amplification (MLPA) to detect deletions in selected genes with recurrent deletions in B-ALL. Methods, analyses, and pipelines are as previously described with cases assigned either adverse (AR) or standard (SR) genomic risk independent of outcome.[11]

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ALL09 has been previously presented in part at the 64th ASH Annual Meeting and Exposition, New Orleans, December 2022, in poster format and at the 29th EHA Congress, Madrid, June 2024, as an oral presentation.

Treatment protocol

A summary of the ALL09 protocol is outlined in Figure 1. ALL09 was based on ALL06 with the following modifications: (i) pegaspargase was dose-reduced for patients with high body mass index (BMI) and hepatic steatosis/dysfunction, and (ii) two 28-day cycles of blinatumomab replaced the cyclophosphamide, cytarabine, and mercaptopurine or thioguanine containing consolidation blocks in ALL06 (i.e., consolidation protocol I and re-consolidation protocol II). Intrathecal (IT) methotrexate was administered on days 1, 12, 24, 36, and 64 in protocol I and on day 64 in protocol II to avoid co-administration with blinatumomab.[27]

In protocol I, after completion of a standard 4-drug induction, all patients were to receive blinatumomab as consolidation therapy between day 36 and day 64 following a TP1 BM aspirate. A TP2 BM aspirate was then performed at day 79 for remission and MRD assessment. Patients who could not tolerate blinatumomab received standard ALL06 chemotherapy. TP1 and TP2 MRD samples were analyzed and reported concurrently to determine risk stratification.

Risk groups are outlined in Supporting Information S8: Table S1. In ALL06 and 09, patients lacking other risk factors were required to achieve TP2 MRD^{neg} to be classified as either clinical standard (CSR) or medium-risk (MR). ALL09 included a "medium/high-risk, poor prednisone response (MHR [PPR])" group to account for the expected increase in PPR patients who also achieved TP2 MRD^{neg}. These patients were offered intensified therapy with two high-risk (HR) block treatments following consolidation but were not routinely offered SCT.[28] In both ALL06 and 09, TP2 MRD^{pos} in association with other criteria classified patients as either medium/high-risk (MHR) or HR if MRD < 5×10^{-4} or very high-risk (VHR) if MRD > 5×10^{-4}.

Patients who were CSR and MR moved to protocol M (high-dose methotrexate). Those considered MHR or higher completed a minimum of two HR block treatments before moving to SCT. MHR or higher patients not proceeding to SCT moved to protocol II (delayed intensification). Protocol II comprised a BFM-based re-induction (days 1–35) followed by a 28-day cycle of blinatumomab at 28 μg/day commencing on day 36 in place of re-consolidation. Maintenance therapy consisted of daily 6-mercaptopurine and weekly oral methotrexate with a total treatment duration not exceeding 24 months from diagnosis.

Statistical methods

An optimal Simon's 2-stage design was used for initial sample size calculation. The level of significance was set to 0.05 with a one-sided test. The primary endpoint was TP2 MRD^{neg} set to 60% under the null, and 78% under the alternative hypotheses. The lower limit of response was set using an interim analysis of the estimated TP2 MRD^{neg} rate from ALL06, with the upper limit based on outcomes from the BLAST study.[8,14,29,30] Using these parameters, the required sample size at the end of stage 2 was 47 patients. The stage 1 futility analysis required a sample size of 16 patients; if 10 or fewer patients were TP2 MRD^{neg}, then the trial would be stopped for futility. At final analysis, if 33 or fewer patients were TP2 MRD^{neg}, then the null hypothesis would be retained. With these settings, the exact probability of a type 1 error under the null hypothesis was 0.0454; the power to reject the null hypothesis under the

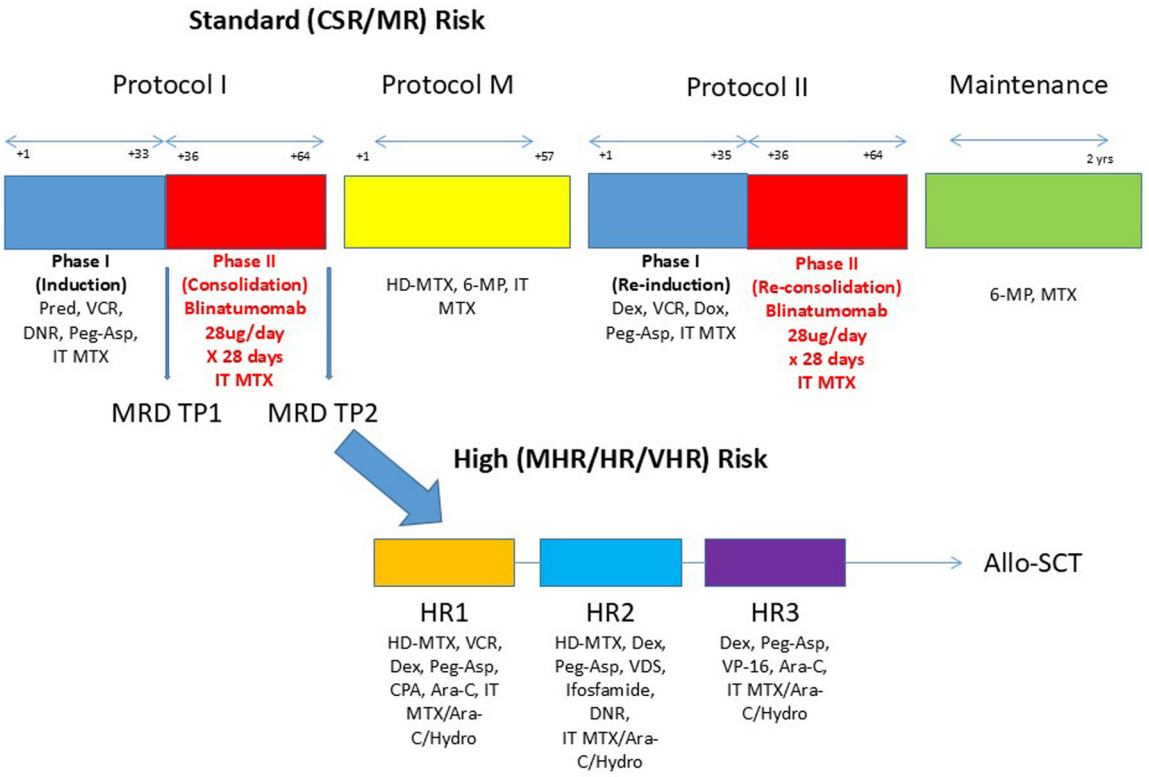

FIGURE 1 **ALL09 protocol summary schema.** The protocol replaced standard chemotherapy for blinatumomab in consolidation. Patients considered medium-high risk (MHR) or greater proceeded to high-risk (HR) block and chemotherapy with allogeneic transplantation if suitable. Clinical standard-risk (CSR) and medium-risk (MR) patients proceeded to high-dose methotrexate and an additional blinatumomab cycle in re-consolidation in minimal residual disease (MRD) negativity. For patients not proceeding to allogeneic transplantation, the protocol was completed in 24 months. VHR, very high risk.

alternative hypothesis was 0.8010. All registered participants were included in intention-to-treat (ITT) survival analyses. The primary endpoint of TP2 MRD^{neg} was assessed using a modified intention-to-treat (mITT) population consisting of all ITT patients who commenced blinatumomab in consolidation with an MRD marker available for assessment at TP2. Continuous variables were summarized as *n*, mean, standard deviation, 95% CI, or range (minimum–maximum). Categorical variables were summarized as frequencies, percentages, and exact 95% CI. For DFS, the time to event was measured from the date of registration to the earliest of date of relapse, death, or, for those without an event, date of last follow-up. For OS, the time to event was measured from the registration date to the time of death or censored at the date of last follow-up. The distribution of the time to event variables such as OS or DFS was estimated with the Kaplan–Meier (KM) method. TP survival estimates with 95% CI, such as 3-year OS, were estimated from KM curves. The Cox Proportional Hazard model was used to test the null hypothesis of equal survival distributions for subgroups of interest, and to estimate the hazard ratio (HzR) with 95% CI.

Data sharing

Deidentified individual participant data will be made available 3 months after publication for a period of 5 years at allg.org.au. Proposals for access should be sent to info@allg.org.au. The ALL09 protocol version 5.0 (14 November 2022) is included as Supporting Information S1 available with the online version of this article.

Genomic data files are available via EGA Accession #EGAS50000001109.

RESULTS

Patient characteristics

A total of 55 patients were registered and commenced ALL09, constituting the ITT cohort (Figure 2). Demographic and pre-treatment characteristics are summarized in Table 1. Median age was 25 (range, 16–38) years. In total, 54.5% patients were male. Mean BMI was 27.0 kg/m^2 (range, 16.0–50.0). Immunophenotype was consistent with pre-B (CD10 positive) in 90.9%, pro-B (CD10 negative) in 3.6%, and not classified in 5.5%. Median follow-up for the cohort was 42.9 (range, 1.9–54.7) months.

Outcomes of the Simon's 2-stage design and end-consolidation (TP2) MRD negativity rate

The mITT cohort consisted of 48 patients; 7 ITT patients were excluded—5 with no MRD marker, 1 induction death, and

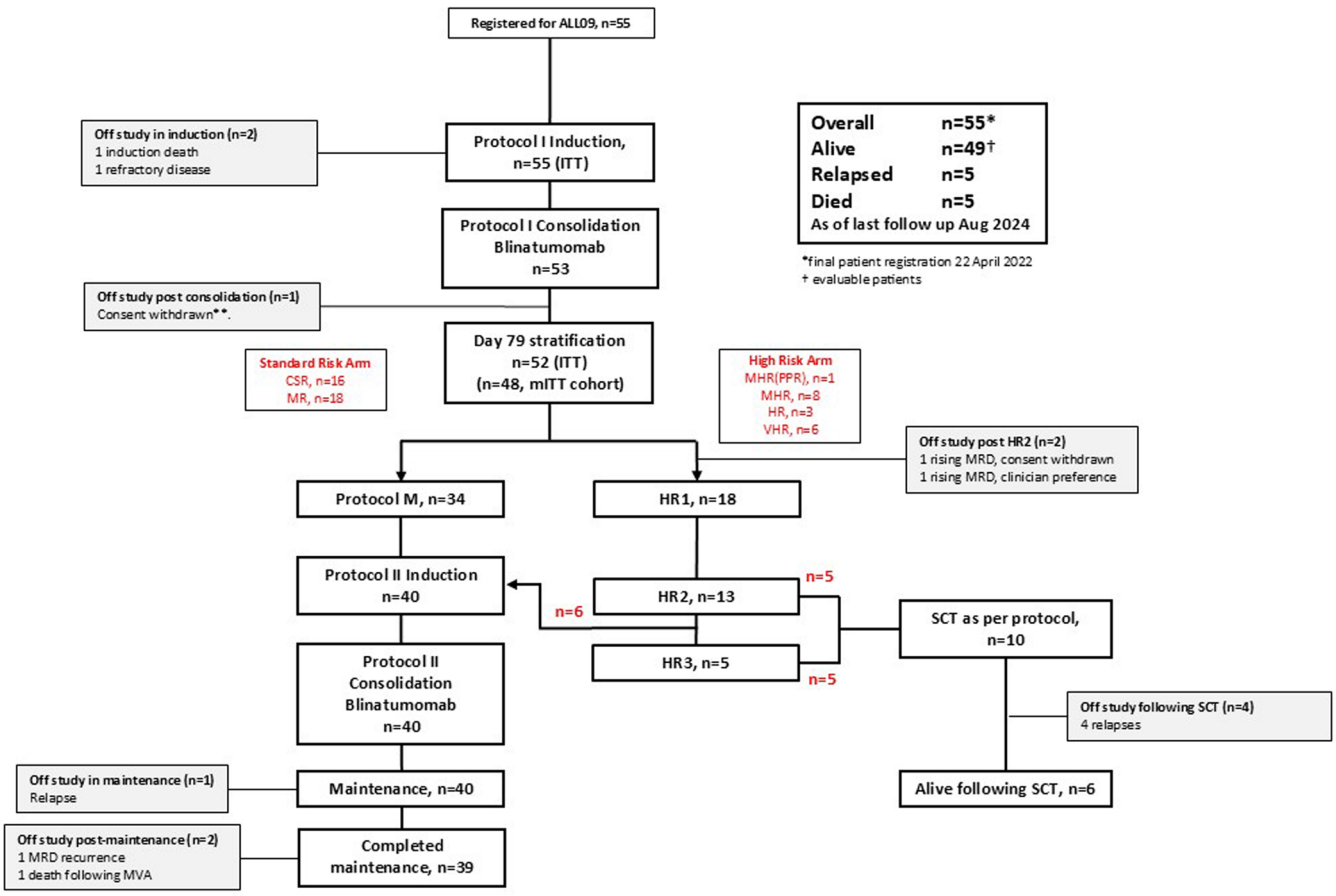

FIGURE 2 **CONSORT diagram outlining outcomes for the 55 patients registered to the Australasian Leukaemia and Lymphoma Group (ALLG) ALL09 study.** From 55 registered patients in the intention-to-treat (ITT) cohort, one patient died from sepsis and one patient was removed from the study with refractory disease in protocol I induction. Five patients had no minimal residual disease (MRD) marker—one patient with no MRD marker withdrew post protocol I consolidation with persistent CNS disease and did not receive blinatumomab**—leaving 48 patients in the modified intention-to-treat (mITT) cohort. CNS, central nervous system; CSR, clinical standard risk; HR, high risk; MHR, medium-high risk; MR, medium risk; MVA, motor vehicle accident; SCT, stem cell transplantation; VHR, very high risk.

TABLE 1 Patient characteristics.

Characteristic	*N* (%) Total *N* = 55 (100)
Gender	
Male	30 (54.5)
Female	25 (45.5)
Age (years)	
Median (range)	25 (16–39)
BMI (kg/m^2)	
Mean (range)	27 (16–50)
<30	38 (69.1)
≥30	17 (30.9)
ECOG performance status	
0	30 (54.5)
1	23 (41.8)
2	2 (3.6)
ALL WHO classification	
B-lymphoblastic leukemia/lymphoma, NOS	33 (60.0)
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	4 (7.3)
t(v;11q23.3); *KMT2A* rearranged	1 (1.8)
t(12;21)(p13.2;q22.1); *ETV6::RUNX1*	6 (10.9)
Hyperdiploidy	5 (9.1)
Hypodiploidy	3 (5.5)
t(1;19)(q23;p13.3); *TCF3::PBX1*	2 (3.6)
BCR::ABL1-like iAMP21	1 (1.8)
CNS disease	
Yes	7 (12.7)
No	48 (87.3)
Presenting WBC (×10^9/L)	
<100	51 (92.7)
≥100	1 (1.8)
Unknown	3 (5.5)
Day 79 risk stratification[a]	
Clinical standard	16 (30.8)
Medium	18 (34.6)
Medium high	8 (15.4)
Medium high (PPR)	1 (1.9)
High	3 (5.8)
Very high	6 (11.5)
Karyotype	
t(4;11)(q21;q23)[b]	4 (7.3)

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; PPR, poor prednisone response; WBC, white blood count; WHO, World Health Organization.

[a]Fifty-two patients were available for day 79 risk stratification.

[b]As assessed by standard karyotype and/or fluorescent in situ hybridization (FISH).

1 patient with progressive disease withdrawn from the study at the investigator's discretion. One mITT patient withdrew consent following HR block 2 and was censored for survival at withdrawal.

TABLE 2 Protocol I minimal residual disease (MRD) response modified intention-to-treat (mITT) cohort.

MRD response	*N* (%) Total (*N* = 48)[a] TP1	TP2
Negative	14 (29.2)	34 (70.8)
Low positive	19 (39.6)	10 (20.8)
Positive	14 (29.2)	4 (8.3)
Unknown	1 (2.1)	0 (0)

[a]Fifty patients had an MRD marker identified at diagnosis. One patient deceased in induction, and one patient was withdrawn for progressive disease before time point 1 (TP1).

In stage 1 of the 2-stage design, 11 of 16 patients achieved TP2 MRD^{neg}, exceeding the futility boundary, and the study proceeded to stage 2. A total of 48 patients were enrolled before the stage 2 analysis, exceeding the prespecified sample size by 1 patient due to the delay in assessing the primary endpoint at day 79. As a result, the probability of a type I error was recalculated under the null hypothesis, assuming an exact binomial distribution conditional on the observed data. At the completion of stage 2, the observed TP2 MRD^{neg} rate was 70.8% (95% CI, 55.9–83.0) or 34 MRD^{neg} responses, enabling rejection of the null hypothesis (P = 0.037). Of the 14 patients who remained TP2 MRD^{pos}, 10 (19.2%) had MRD < 5×10^{-4} and 4 (7.7%) had MRD ≥ 5×10^{-4}. Table 2 outlines MRD responses at TP1 and TP2 in the mITT cohort. In those with a TP1 result (n = 47), TP1 MRD^{neg} rates in ALL09 did not differ significantly from the B-cell cohort in ALL06 (14/47 vs. 8/50, P = 0.105).

Induction outcomes

CR was achieved in 95.7% of evaluable ITT patients at TP1. Of 52 evaluable patients at TP2, 100% achieved CR. One patient (1.8%) died from sepsis before commencement of blinatumomab in protocol I after spontaneous delivery of a live infant at 34 weeks of gestation. One patient had progressive disease and was withdrawn at the investigator's discretion before receiving blinatumomab. One patient with persistent CNS disease at day 36 and no MRD marker received protocol I consolidation chemotherapy before withdrawing consent. There were no treatment-related deaths beyond protocol I induction (Figure 2).

Protocol I deliverability and blinatumomab tolerability

In ALL09, 82.7% of B-lineage patients commenced protocol M or HR1 (M/HR) by day 94 versus 45.1% in ALL06 (P < 0.0001). In evaluable patients, median time to protocol M or HR therapy in ALL09 was 84 days (range, 77–134) versus 97 days (range, 87.5–103) (HzR 2.19, 95% CI, 1.47–3.27, P = 0.0001) in ALL06 (Supporting Information S2: Figure S1). Blinatumomab was generally well tolerated with 41 Grade 3 or 4 events in 22 patients during protocol I consolidation, including fever (n = 1), headache (n = 1), seizure (n = 1), and stroke (n = 1). In protocol II consolidation, there were 13 Grade 3 or 4 events reported in 10 patients, including cytokine release syndrome (n = 2), confusion (n = 1), and delirium (n = 1). All Grade 3 and 4 events in protocol I and II are outlined in Supporting Information S8: Table 2. All eligible patients were able to complete the scheduled 2 × 28-day blinatumomab cycles.

Mortality, DFS, and OS

In the ITT cohort, 48 (90.4%) participants were alive, and 5 (9.6%) had died (1 treatment-related, 3 relapse, 1 motor vehicle accident (MVA)

in CR) with 2 patients withdrawn from study at last follow-up. Five patients have relapsed, all with BM disease. In addition, two patients became MRD^{pos} following HR2 and were taken off study. One of these patients withdrew consent for follow-up and was censored at withdrawal. One patient had BM MRD recurrence following completion of maintenance. All five morphological relapses occurred after HR therapy, with four occurring after SCT in CR1. Three relapsed patients have deceased, and two remain alive at the last follow-up. In the ITT cohort, the estimated 3-year DFS was 88.6% (95% CI, 76.3%–94.7%) and estimated 3-year OS was 90.5% (95% CI, 78.6%–95.9%) (Figure 3). In the mITT cohort, the estimated 3-year DFS and OS was 91.1% (95% CI, 78.0%–96.6%) and 93.3% (95% CI, 80.5%–97.8%), respectively (Supporting Information S3: Figure S2). In the TP2 MRD^{neg} cohort, both 3-year DFS and OS was 96.7% (95% CI, 78.6%–99.5%) versus 3-year DFS 76.9% (95% CI, 44.2–91.9, HzR 0.23, P = 0.11) and 3-year OS of 84.6% (95% CI, 51.2%–95.9%, HzR 0.18, P = 0.16) in the MRD^{pos} cohort (Supporting Information S4: Figure S3).

Risk stratification

Fifty-two patients were available for risk stratification at TP2 (including four without an MRD marker). Sixteen (30.8%) were CSR, 18 (34.6%) were MR, 8 (15.4%) were MHR, 1 (1.9%) was MHR (PPR), 3 (5.8%) were HR, and 6 (11.5%) were considered VHR (Table 1). The CSR/MR cohort had 3-year DFS and OS of 96.7% with the single death secondary to an MVA in CR1 having completed all protocol treatment. Final risk groupings differed significantly (P = 0.007) from the B-cell cohort in ALL06 (n = 50) as outlined in Table 3.

Impact of HR therapy and SCT outcomes

Eighteen patients proceeded to HR blocks and received at least one cycle of HR therapy. Of these, two were considered MHR (PPR), eight MHR, two HR, and six VHR. Sixteen had an MRD marker available at HR block entry, of which 14 were MRD^{pos}. Following HR1, 12/16 achieved MRD^{neg}. Following HR2, only 9/16 remained MRD^{neg}. Five patients received HR3; four had an MRD marker, with two being MRD^{neg} on final assessment before SCT. Ten patients proceeded to SCT in first CR. Five proceeded to matched sibling SCT, four matched unrelated SCT, and one to haploidentical SCT. Of the 10 patients proceeding to SCT, 4 have relapsed, with 2 relapse deaths and no non-relapse mortality as of last follow-up. As per protocol, MHR patients who achieved MRD^{neg} following HR therapy but lacked a sibling donor (n = 5) or were considered MHR (PPR) (n = 1) returned to protocol II after completing HR blocks (Figure 1). Of these, one MHR patient relapsed during maintenance after achieving MRD^{neg} following HR therapy and deceased following a second relapse post-SCT. The remaining five patients who returned to protocol II are alive and disease-free as of last follow-up.

Genomic analysis

Of 55 ITT patients, 46 had samples available for diagnostic genomic analysis (Figure 4). Based on the criteria used in ALL06, 33 patients (71.7%) were considered to have AR and 13 (28.3%) SR lesions.[11] In a post hoc analysis, SR patients had 3-year OS and DFS of 100%. AR patients had 3-year DFS 80.6% (95% CI, 61.8%–90.8%) and OS 83.8% (95% CI, 65.3%–92.9%) (Supporting Information S5: Figure S4). All four morphologic relapses in the genomic cohort occurred in the AR group (hypodiploid = 1, *PAX5*alt = 1, and *TCF3::PBX1* = 2). All five deaths were in the AR cohort—one induction death (CDX2 high), three relapse deaths (*PAX5*Alt = 1, *TCF::PBX1* = 1, and hypodiploid = 1), and one MVA in remission (hypodiploid). Of the seven SCT patients in the genomic cohort, four were AR (hypodiploid = 1, *KMT2Ar* = 2, and *TCF3:PBX1* = 1). Of the four *PAX5* p.P80R patients, three remained TP2 MRD^{pos} accounting for the remaining three SCT patients in the genomics cohort. These *PAX5* p.P80R patients also had deletions of *CDKN2A/B* and *PAX5*, with two also having *IKZF1* deletions, being also classified as $IKZF1^{plus}$.

TABLE 3 Final risk groups in B-cell cohort ALL06 versus ALL09.

Protocol	Risk group[a] N (%)				
	CSR	MR	MHR	HR	VHR
ALL06 (n = 50)	6 (12.0)	15 (30.0)	7 (14.0)	1 (2.0)	21 (42.0)
ALL09 (n = 51)[b]	16 (31.4)	18 (35.3)	8 (15.7)	3 (5.9)	6 (11.8)

Abbreviations: CSR, clinical standard risk; HR, high risk; MHR, medium-high risk; MR, medium risk; VHR, very high risk.

[a]Chi-square P = 0.007.

[b]Fifty-two patients had a risk group assigned. MHR(poor prednisone response [PPR]), n = 1 were not included in this analysis as this risk group did not exist in ALL06.

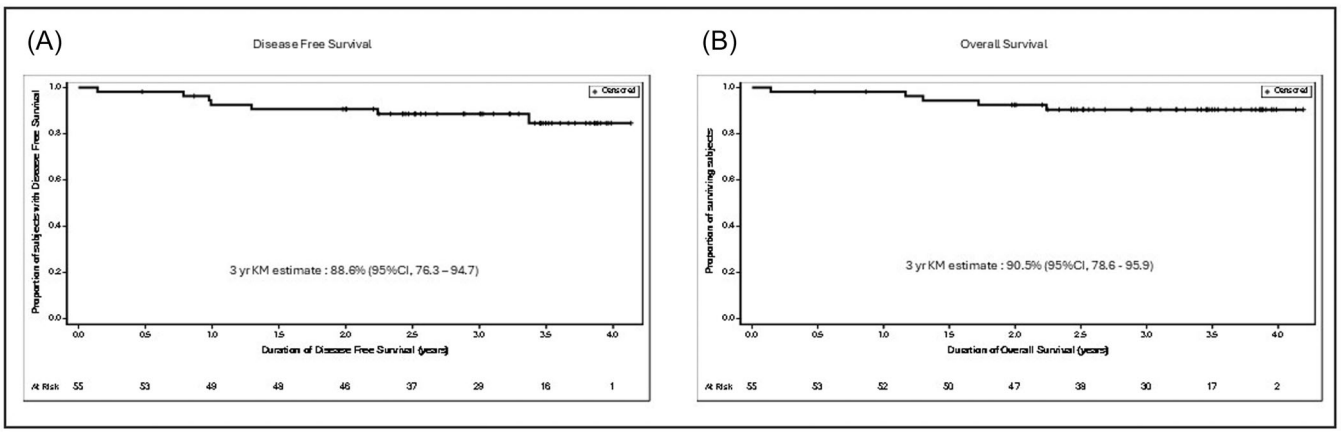

FIGURE 3 **Intention-to-treat (ITT) survival outcomes.** In the ITT cohort, at median follow-up of 42.9 months, 49 (89.1%) participants were alive and 5 (10.9%) had deceased. (A) Kaplan–Meier estimated 3-year disease-free survival (DFS) is 88.6% (95% CI, 76.3–94.7). (B) Kaplan–Meier estimated 3-year overall survival (OS) was 90.5% (95% CI, 78.6–95.9). KM, Kaplan–Meier.

In the genomics cohort, 7 did not have TP2 MRD available, of which 6/7 were AR, including 2 of 4 with *KMT2A*r. Of 39 patients with both genomics and TP2 MRD, 27 (69.2%) were AR. In these 39 patients, 41% were TP2 MRD^{pos}, of which 84.6% were AR. In this cohort, 100% of *KMT2A*r ($n = 2$), 100% *TCF3*::*PBX1* ($n = 3$), 75% *PAX5* p.P80R ($n = 4$), and 66% *DUX4*r ($n = 3$) patients remained TP2 MRD^{pos}. Outcomes by individual genomic lesion are outlined in the accompanying oncoplot (Figure 4).

AR patients achieving TP2 MRD^{neg} ($n = 16$, 59% of AR) had non-inferior 3-year OS and DFS, both 92.9% (95% CI, 59.1–99.9, P = 0.36) versus SR patients. Patients with AR and TP2 MRD^{pos} ($n = 11$, 41% of AR patients) had significantly inferior 3-year DFS of 70% (95% CI, 32.9–89.2,) versus SR patients (100%, P = 0.045) with 3-year OS 80% (95% CI, 40.9–94.6) versus SR cohort (100%, P = 0.112) (Figure 5).

Other predictors of outcome

On univariate analysis, only risk stratification greater than CSR/MR was associated with poorer 3-year DFS (HzR 10.7, 95% CI, 1.25-91.78, P = 0.031) but not OS (Supporting Information S8: Table S3). DFS and OS outcomes by risk group are outlined in Supporting Information S7: Figure S6.

DISCUSSION

This study demonstrates that replacing standard consolidation chemotherapy with blinatumomab in a pediatric ALL protocol is associated with high rates of end-consolidation MRD^{neg}, improved on-time protocol progression, and excellent survival in an AYA population. We also demonstrate that SR patients have exceptional survival outcomes using this approach, while AR, TP2 MRD^{pos} patients continue to have poorer DFS despite intensified therapy and SCT.

The efficacy of blinatumomab added to chemotherapy has been demonstrated in previous de novo Philadelphia-negative ALL trials. The addition of a single cycle of post-induction blinatumomab to the Interfant-06 backbone was associated with improved 2-year DFS from 49.4% to 81.6% with a post-blinatumomab MRD^{neg} rate of 53% in 30 patients with infant ALL.[15] In SR pediatric B-ALL, the AALL1731 phase 3 study demonstrated improved 3-year DFS with the addition of blinatumomab to chemotherapy over chemotherapy alone.[16]

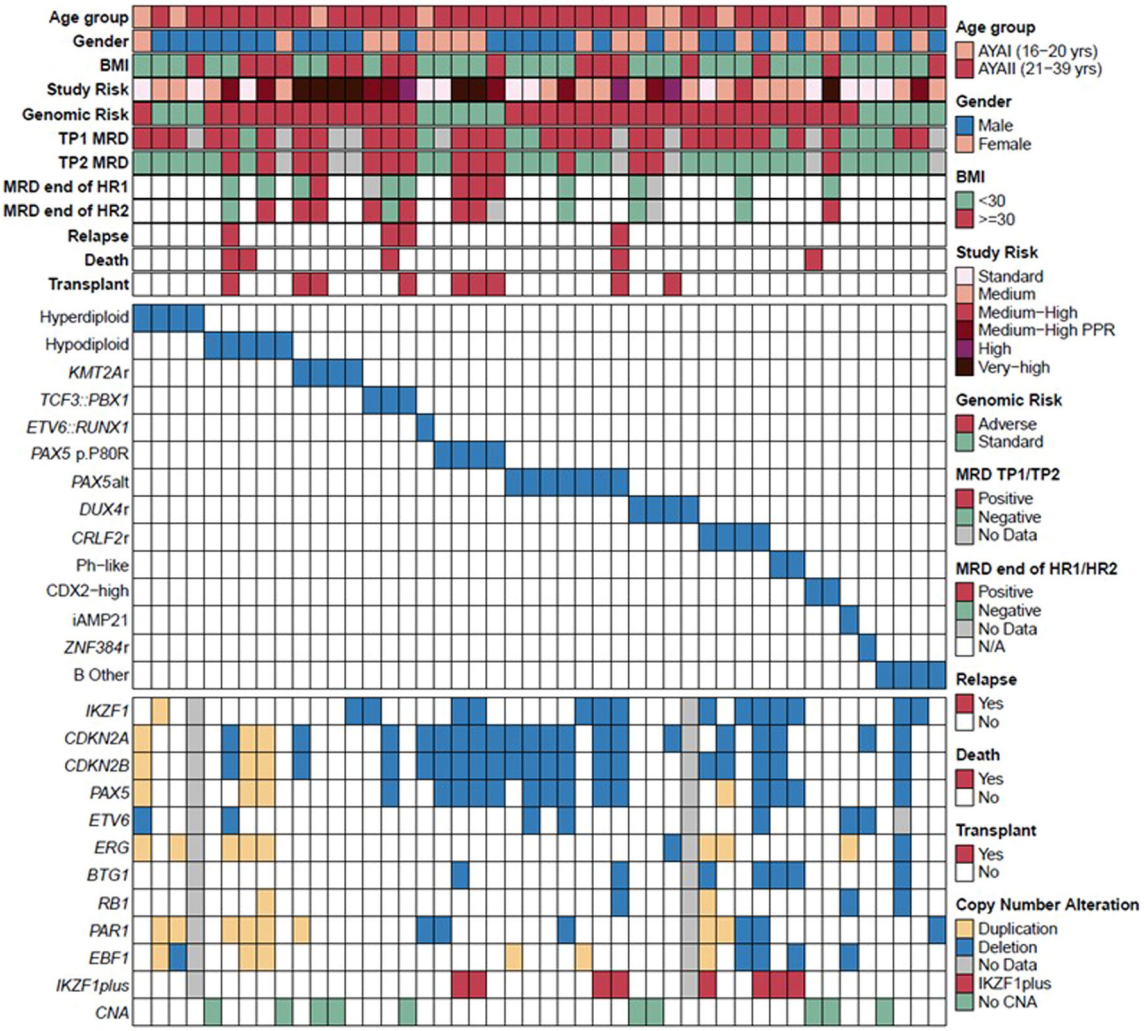

FIGURE 4 **ALL09 oncoplot**. Where minimal residual disease (MRD) was available for patients in the genomics cohort, 100% KMT2Ar ($n = 2$), 100% TCF3-PBX1 ($n = 3$), 75% PAX5 p.P80R ($n = 4$), and 66% DUX4r ($n = 3$) pts remained TP2 MRD^{pos} following exposure to blinatumomab consolidation in protocol I while 100% CRLF2r ($n = 4$) and Ph-like disease ($n = 2$) were TP2 MRD^{neg}. BMI, body mass index; HR, high risk; PPR, poor prednisone response; TP, time point.

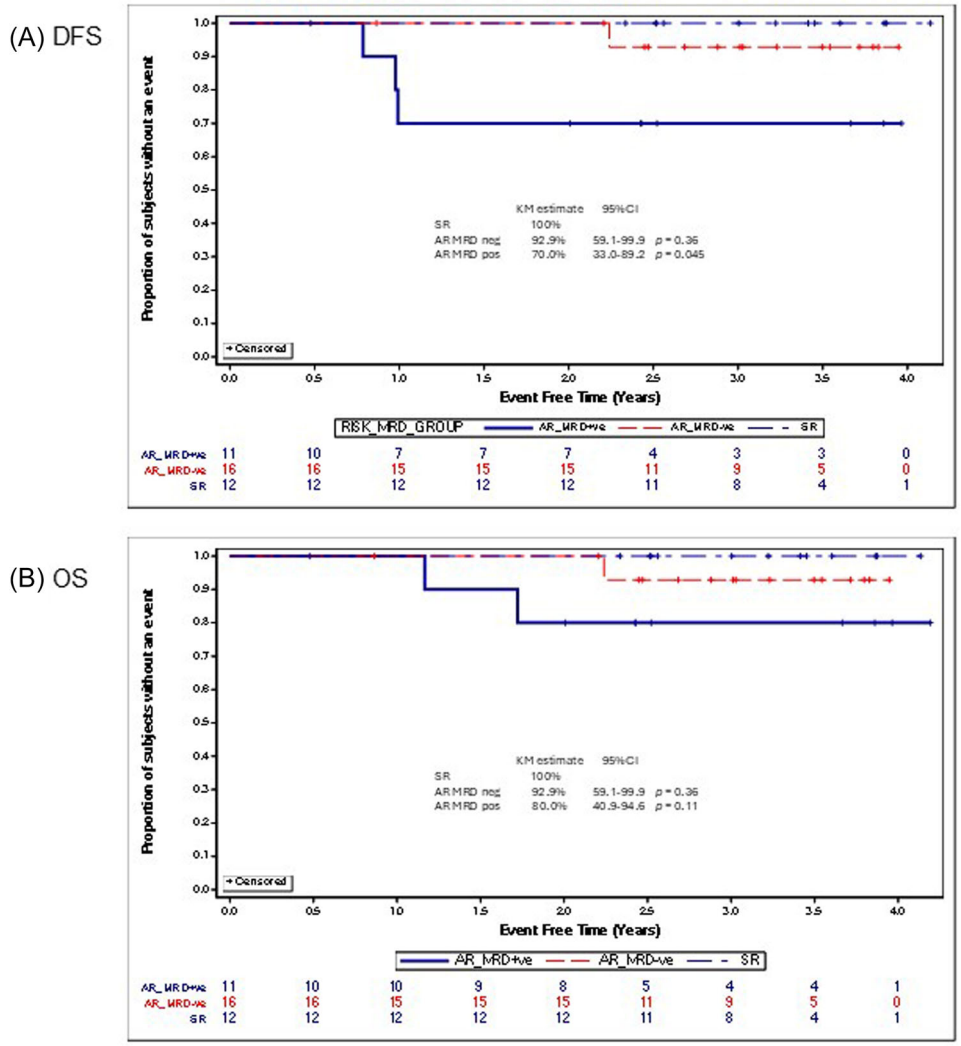

FIGURE 5 **Impact of genomic risk and time point 2 (TP2) minimal residual disease (MRD) on outcomes.** Patients with standard-risk (SR) genomics had 100% 3-year disease-free survival (DFS) and overall survival (OS). Patients with adverse risk (AR) genomics who were TP2 MRD negative had similar 3-year DFS and OS to SR patients (92.9%, 95% CI, 59.1–99.9, P = 0.36). (A) AR patients who were TP2 MRD positive had significantly poorer 3-year DFS (70.0%, 95% CI, 33.0–89.2, P = 0.045). (B) AR patients had an OS of 80% (95% CI, 40.9–94.6, P = 0.112) versus SR patients. KM, Kaplan–Meier.

E1910 added four cycles of blinatumomab to the E2993 backbone in a randomized study of patients aged 30–70 years who achieved MRD^{neg} assessed by flow cytometry, demonstrating a survival advantage for those receiving blinatumomab in the MRD^{neg} setting.[23] In an earlier, older adult ALLG study, sequential blinatumomab and chemotherapy was associated with a 93% CR rate following the first blinatumomab/chemotherapy sequence.[21] In addition, in the LAL2317 study, the addition of two cycles of blinatumomab to a chemotherapy backbone was associated with particularly favorable outcomes in the 18–40 year age group.[22] However, our study is the first to assess the utility of substituting blinatumomab entirely for consolidation chemotherapy in an intensive pediatric protocol.

The ALL09 protocol has potential advantages in the de novo ALL setting. Our study design was informed by results from ALL06, suggesting the majority of AYA patients would be MRD^{pos} at TP1, and results from the BLAST study in MRD^{pos} disease so that all patients would receive blinatumomab in protocol I to improve day 79 (TP2) MRD^{neg} rates. In BLAST, most responses to blinatumomab were seen in the first cycle with a complete MRD response associated with a significant improvement in OS. In ALL09, we assumed equipoise in offering standard cytotoxic HR therapy to blinatumomab non-responders based on our experience with ALL06, and on the results from BLAST suggesting <2% additional complete MRD responses beyond the first cycle of blinatumomab.[14] However, for blinatumomab responders, we presumed a benefit of additional blinatumomab in protocol II. Subsequent studies appear to support this approach with E1910 demonstrating a survival advantage with the use of blinatumomab in the MRD^{neg} setting and 3-year DFS of 92% in the younger patient cohort in LAL2317 who achieved early MRD^{neg} before the first blinatumomab block.[22,23] In addition, we saw encouraging outcomes using only two courses of blinatumomab in contrast to other studies involving multiple cycles.[20,21] We also used a delayed, non-sequential blinatumomab schedule to improve efficacy in a cohort likely to have achieved CR and to minimize the risk of T-cell exhaustion arising from continuous blinatumomab exposure.[13,14,31] Furthermore, replacing conventional consolidation chemotherapy with blinatumomab may reduce toxicity and associated hospitalization costs. In the current study, blinatumomab was associated with

more rapid progression to protocol M/HR than in our ALL06 study. Time to M/HR was used as a toxicity surrogate in ALL06, and treatment interruption and delay have been associated with inferior OS, particularly in patients proceeding to SCT.[32] A comparative analysis of ALL06 versus ALL09 toxicity is planned with more mature follow-up in the ALL09 cohort.

We saw significant differences in risk group stratification between ALL09 and the B-cell cohort in our previous ALL06 study. Final risk group stratification was dependent on multiple factors, including the level of TP2 MRD (Supporting Information S8: Table S1). In ALL09, it is notable that TP2 MRD > 5×10^{-4} was seen in 4/48 (8.4%) patients versus 10/51 (19.6%) B-lineage patients in ALL06 with a corresponding increase in the TP2 MRD^{neg} rate in ALL09 (Supporting Information S8: Table S4). Small numbers limit the significance of these findings but suggest that the inclusion of blinatumomab in consolidation may impact risk criteria developed using chemotherapy-based treatments, reducing the number of patients requiring more intensive therapy and SCT. Whether the inclusion of blinatumomab as standard of care in the management of de novo disease impacts the prognostic relevance of these "classical" risk groups will require longer follow-up.

Our study was not powered to demonstrate the impact of TP2 MRD on survival, but outcomes in the TP2 MRD^{neg} cohort were excellent with a single death related to a non-relapse off-treatment event. In contrast, the cohort remaining MRD^{pos} after the first three cycles of LAL1913-based chemotherapy in LAL2317, but achieving MRD^{neg} after the first blinatumomab cycle had a 3-year DFS of 22%. Earlier incorporation of blinatumomab after cytotoxic induction may improve the outcome of some chemotherapy-insensitive AR disease (such as Ph-like) that appeared enriched in the early MRD^{pos} cohort in LAL2317 and may be more sensitive to bispecific therapy, but this approach may still have less impact on other AR disease, such as *KMT2Ar*, which may be less sensitive to blinatumomab.[22] Outcomes for those with BMI ≥ 30 kg/m^2 compared favorably to our ALL06 study, suggesting this approach may be beneficial in this cohort (Supporting Information S6: Figure S5).[8,33,34] Diagnostic genomics stratified by MRD was predictive of DFS. SR was associated with 100% TP2 MRD^{neg} and 100% survival. AR in association with MRD^{pos} was associated with significantly poorer DFS, although outcomes appear improved compared to those seen in ALL06 (RFS 50%, OS 44%).[11] Small numbers limit our conclusions regarding individual genomic lesions, but it is notable that 3 of 4 *PAX5* p.P80R patients remained TP2 MRD^{pos}. Previous reports had suggested this lesion should be regarded as SR in adults. However, other reports have suggested inferior outcomes in younger patients with relapse risks approaching those of some Ph-like cohorts.[35,36]

For most MRD^{pos} patients at TP2, we found that additional cycles of intensified chemotherapy were of modest benefit, with four of eight SCT patients with an MRD marker remaining positive before SCT. In addition, 4/5 relapses occurred post-SCT, suggesting that alternative strategies will be required for those who remain MRD^{pos} following blinatumomab consolidation. In the limited number of patients who were MHR and did not proceed to SCT or those who were MHR (PPR), protocol II reinduction followed by consolidation with blinatumomab in the MRD^{neg} state appeared to be a promising strategy with only one of six of these patients relapsing as of last follow-up. The optimal approach to low-level post-blinatumomab MRD^{pos} in the de novo setting is unclear, but our findings suggest that it may be possible to avoid SCT in this cohort if additional blinatumomab is offered following the achievement of MRD^{neg}.

We used RQ-PCR for MRD assessment. Most published data for MRD assessment in childhood and adult ALL is based on RQ-PCR, a highly validated and standardized technology within the EuroMRD Consortium, making our results broadly applicable across study groups.[37] RQ-PCR is regarded as more sensitive than flow cytometry but may be less specific than next-generation sequencing (NGS) at very low levels of residual MRD considered positive but non-quantifiable by RQ-PCR.[38,39] However, studies to date have suggested that MRD^{neg} as assessed by RQ-PCR is generally confirmed by NGS and is prognostically favorable.[39] Of note, no TP2 MRD^{neg} patient had relapsed in our cohort by data cutoff, suggesting RQ-PCR was a highly sensitive assay in the context of this study. RQ-PCR is associated with a 5%–10% failure rate due to biological or technical factors and may be more susceptible to clonal evolution associated with false negative results.[40] NGS may have improved our MRD technical failure rate, which was 12.7%. This included two patients with *KMT2Ar* disease, where detection of IgH/TCR-based clonality by RQ-PCR may be more challenging.[41]

Our study suggests that substituting blinatumomab for conventional consolidation chemotherapy in de novo B-lineage AYA ALL is associated with improved MRD^{neg} rates and excellent survival, particularly in clinical and genomic standard-risk cohorts. Patients achieving end-consolidation MRD^{neg} with SR genomics have high DFS and OS using this approach. Further studies are required to identify whether specific AR genomic subtypes may be less sensitive to blinatumomab consolidation. We suggest that blinatumomab substitution for standard chemotherapy be considered an alternative strategy in future randomized studies in AYA ALL. Proposed ALLG trials will incorporate genomically targeted therapies to improve outcomes in those remaining MRD^{pos} following protocol I blinatumomab consolidation.

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review and editing. **Michael Osborn**: Conceptualization; resources; writing—original draft; writing—review and editing. **Ashley P. Ng**: Resources; writing—original draft; writing—review and editing. **Shaun Fleming**: Conceptualization; resources; writing—original draft; writing—review and editing. **Pasquale Fedele**: Resources; writing—original draft; writing—review and editing. **Toby Trahair**: Conceptualization; writing—original draft; writing—review and editing. **John Casey**: Writing—original draft; writing—review and editing. **Sally Mapp**: Resources; writing—original draft; writing—review and editing. **Carol Cheung**: Resources; writing—original draft; writing—review and editing. **Tasman Armytage**: Resources; writing—original draft; writing—review and editing. **Michelle Henderson**: Conceptualization; resources; writing—original draft; writing—review and editing. **Rosemary Sutton**: Resources; writing—original draft; writing—review and editing. **Jacqueline Rehn**: Writing—original draft; writing—review and editing. **Elyse Page**: Writing—original draft; writing—review and editing. **Susan Heatley**: Data curation; formal analysis; writing—original draft; writing—review and editing. **Peter Button**: Conceptualization; writing—original draft; writing—review and editing. **Leesa Rowley**: Writing—original draft; writing—review and editing. **Stephen R. Larsen**: Resources; writing—original draft; writing—review and editing. **Peter Presgrave**: Resources; writing—original draft; writing—review and editing. **John Kwan**: Resources; writing—original draft; writing—review and editing. **Samuel Bennett**: Resources; writing—original draft; writing—review and editing. **Chun Yew Fong**: Resources; writing—original draft; writing—review and editing. **Luciano Dalla Pozza**: Conceptualization; writing—original draft; writing—review and editing. **David Yeung**: Conceptualization; resources; writing—original draft; writing—review and editing. **Deborah White**: Conceptualization; resources; data curation; formal analysis; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

M.G. has served on advisory boards for Amgen, Pfizer, Servier, and Jazz Pharmaceuticals and has received trial and research support from Amgen and Servier. M.O. has served on advisory boards for Amgen. C.Y.F. has served on advisory boards for Adaptive, Amgen, Astellas, Jazz Pharmaceuticals, Otsuka, and Pfizer; has received honoraria/speaker's bureau from AbbVie, Novartis, Pfizer, and Servier; and has received research funding from Amgen and Jazz Pharmaceuticals. L.D.P. has served on advisory boards for Amgen and Jazz Pharmaceuticals.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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