ECOG-ACRIN cancer research group
Reshaping the future of patient care

E1910

This is an FDA Registration Trial

A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-negative B lineage Acute Lymphoblastic Leukemia in Adults

STUDY CHAIR:	Mark R. Litzow, MD
STUDY CO-CHAIR:	Ryan J. Mattison, MD
STUDY STATISTICIAN:	Zhuoxin Sun, PhD
ALLIANCE CO-CHAIR:	Matthew J. Wieduwilt, M.D., Ph.D.
Rev. 7/14 SWOG CO-CHAIR	Michaela Liedtke, M.D.
CCTG CO-CHAIR:	Julie Bergeron, M.D.
BMT CO-CHAIR:	Hillard M. Lazarus, MD
LABORATORY CO-CHAIRS:	Elisabeth Paietta, Ph.D. Charles Mullighan, MD Cheryl Willman, MD
LEUKEMIA COMMITTEE CHAIR:	Martin S. Tallman, MD
PATHOLOGY CO-CHAIR:	Daniel Arber, M.D.
CYTOGENETICS CO-CHAIR:	Yanming Zhang, M.D.

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Rev. 7/14 ***STUDY PARTICIPANTS***

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
Rev. 3/15 **SWOG** / SWOG
CCTG / Canadian Cancer Trials Group

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Addendum #10 - 8/17
Addendum #11 – 9/17
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Addendum #18

Agent	IND	NSC	Supply
Blinatumomab	IND Sponsor DCTD, NCI IND#	765986	NCI
Rev. Add14 IV Solution Stabilizer for blinatumomab		773150	NCI

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STUDY CHAIR

Mark R. Litzow, MD
Division of Hematology
Mayo Clinic
200 First Street, S.W.
Rochester, MN 55905-5905
Phone: (507) 284-6921
Fax: (507) 266-4972
E-mail: litzow.mark@mayo.edu

Rev.6/16, 2/18

STUDY CHAIR LIAISON (SCL)

Jeffrey Hirvela
Mayo Clinic - East 10, Room Ma 10-54W
200 First Street, S.W.
Rochester, MN 55905
Phone: (507) 538-4212
Fax: (507) 284-0658
E-mail: hirvela.jeffrey@mayo.edu

STUDY CO-CHAIR

Ryan Mattison, MD
University of Wisconsin School of Medicine and Public Health
Division of Hematology/Oncology
4039 WIMR
1111 Highland Avenue, MC2275
Madison, WI 53705
Phone: (608) 262-5697
Fax: (608) 262-4598
E-mail: rjmattison@medicine.wisc.edu

ALLIANCE CO-CHAIR

Matthew J. Wieduwilt, M.D., Ph.D.
Division of Bone Marrow Transplantation
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive, #0960
La Jolla, CA 92093-0960
Phone: (858) 822-6848
Fax: (858) 822-6844
E-mail: mwieduwilt@ucsd.edu

Rev. 7/14

SWOG CO-CHAIR

Michaela Liedtke, M.D.
Stanford Cancer Institute
875 Blake Wilbur Dr, Rm 2327B
Stanford, CA 94305
Phone: (650) 498-6000
Fax: (650) 724-5203
E-mail: mliedtke@stanford.edu

Rev. 2/18

CCTG CO-CHAIR

Julie Bergeron, M.D.
Université de Montréal
Hématologie et oncologie
Hôpital Maisonneuve-Rosemont
Phone: (514) 252-3404
Fax: (514) 254-5094
E-mail: juliebergeron.hmr@ssss.gouv.qc.ca

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and supporting and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' websiteis managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinicaldata submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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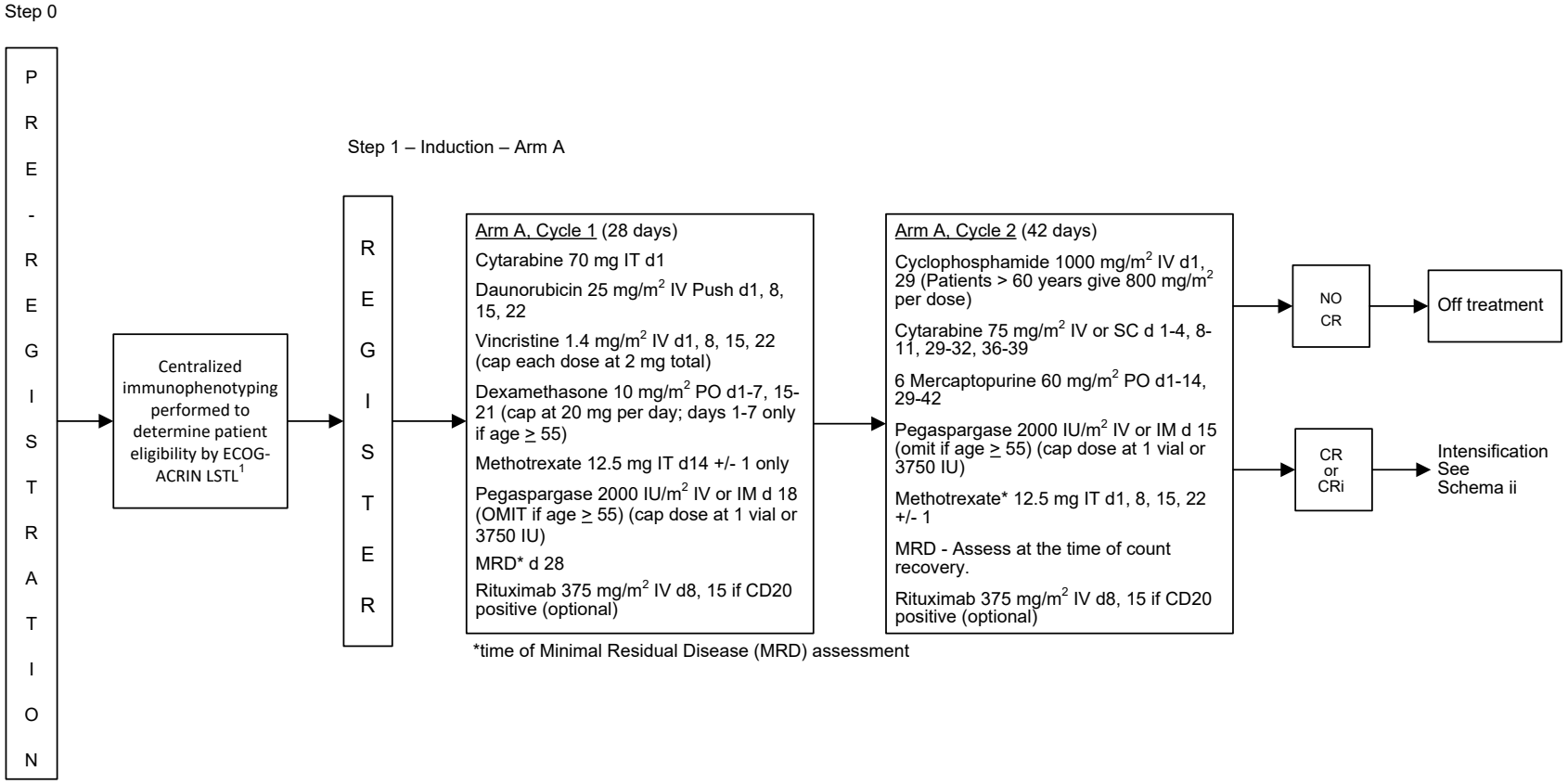
Schema



Total Accrual: 488

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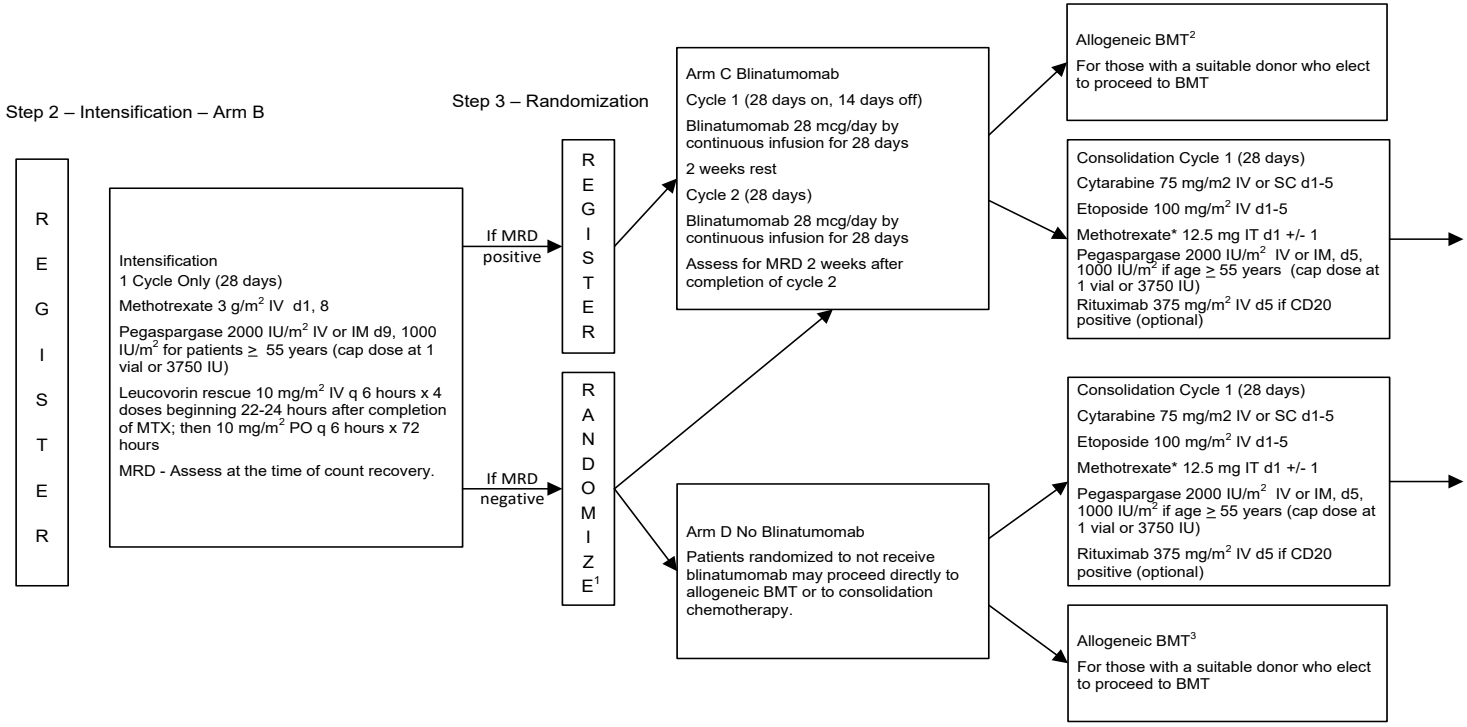
1. Bone Marrow and peripheral blood specimens must be submitted for mandatory testing for participation in this study.

* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Rev.7/14,3/15, 6/16, 8/17

Schema



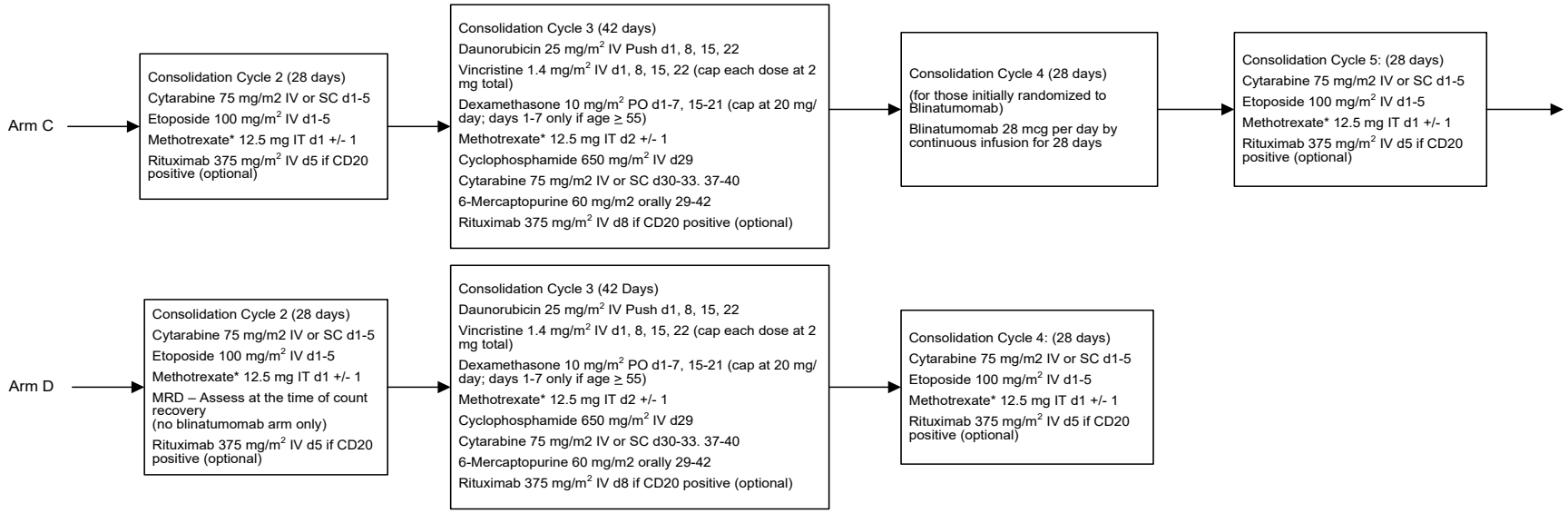
ii

1. Stratification:
   - < 55 yrs. vs ≥ 55 years
   - CD20 status positive vs. negative
   - rituximab use yes or no
   - Intent to receive allogeneic SCT or not
2. Patients may receive up to 2 cycles of consolidation chemotherapy prior to transplant.
   NOTE: Only submit bone marrow aspirates from the FIRST PULL for MRD.
3. Patients may receive up to 3 cycles of consolidation chemotherapy prior to transplant.
   NOTE: Only submit bone marrow aspirates from the FIRST PULL for MRD.

* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Rev.6/16, 8/17

Schema



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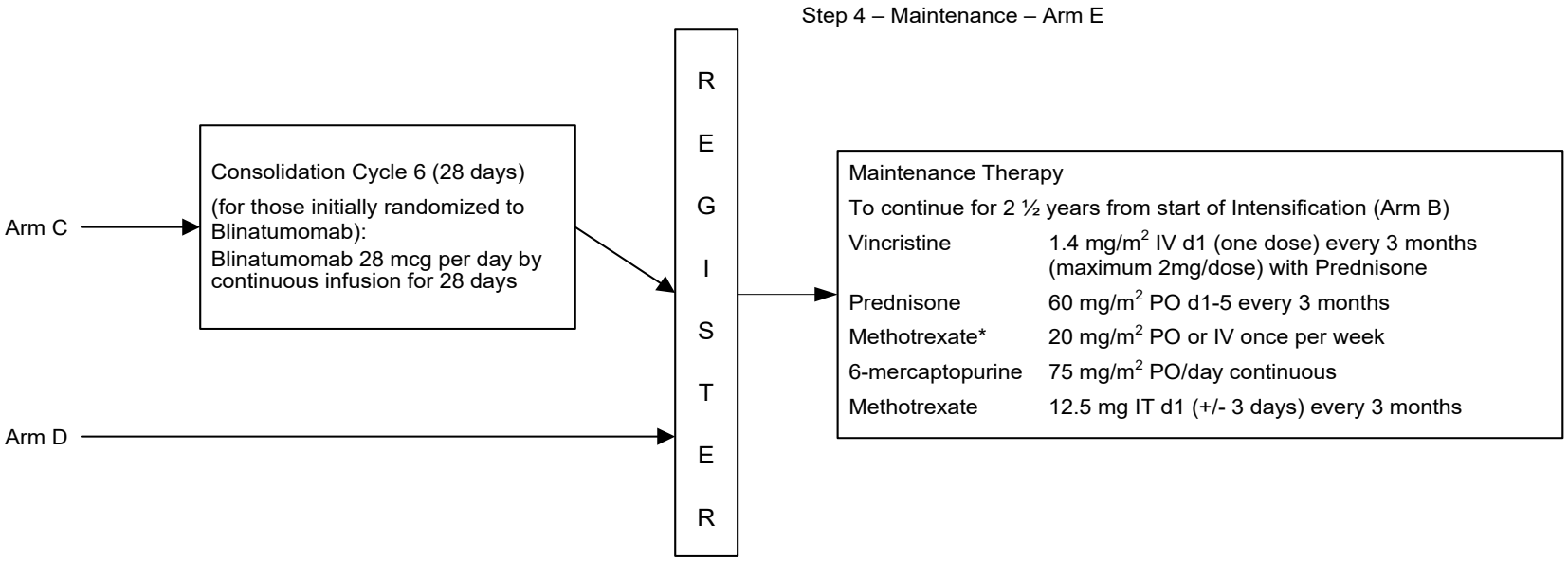
Rev.6/16, 1/17, 8/17

Schema



* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

1. Introduction

1.1 Background:

The treatment of children with ALL is a shining example of the success of combination chemotherapy in curing malignancy. Results of recent trials suggest that up to 90% of children may be cured of their disease[1]. Adult patients with ALL now have a 90% chance of entering first complete remission (CR) with modern chemotherapy[2]. However, most patients still relapse, and leukemia-free survival with three to seven years of follow-up is only 30-40% [2]. The poor outcome of chemotherapy in adults with ALL as compared to children relates to multiple factors, some of which are known but others which remain unknown. It is known that older adults with ALL do not tolerate intensive courses of chemotherapy as well as children and pediatric protocols tend to contain much higher doses of selected drugs. Also adults have a higher incidence of poor prognostic subtypes of ALL such as BCR-ABL ALL and a lower incidence of favorable subtypes such as the t(12;21)subtype[3,4].

The Medical Research Council, MRC, now known as the National Cancer Research Institute (NCRI), in Great Britain and the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) in the United States have conducted the largest trial in adult ALL ever reported, UKALLXII/E2993, for patients 65 years of age or younger. All patients received two months of intensive induction chemotherapy followed by one month of intensification with high-dose methotrexate and L-asparaginase. Patients under the age of 55 with an HLA-matched sibling were assigned to allogeneic SCT. All other patients were randomized between autologous SCT and consolidation/maintenance therapy for 2.5 years. Standard risk patients were defined as those patients who were either less than 35 years of age, achieved a remission after less than four weeks of therapy, had leukocyte count less than 30 x 10^9/L for B cell type and less than 100 x 10^9/L for T cell type or lacked a BCR-ABL gene rearrangement, 11q23 abnormality, t(4;11) or t(1;19). All other patients were considered high risk. An analysis of 1,913 patients was reported. The CR rate for the BCR-ABL negative patients was excellent at 90%. For the comparison between autologous SCT and chemotherapy 456 patients were randomized, 229 to autologous transplant and 227 to chemotherapy. The two groups were well balanced for age, gender, leukocyte count at diagnosis and immunophenotype. Event-free survival (EFS) at five years from the time of diagnosis or randomization was 41% for the chemotherapy group and 32% for the autologous group (p=0.02). Overall survival (OS) also favored chemotherapy (46%) compared to autologous SCT (37%) (p=0.03) [5].

Important analyses from the study have compared the outcome of BCR-ABL-negative patients assigned to HLA-matched sibling SCT compared to patients randomized to autologous SCT or chemotherapy (donor vs. no donor). In a comparison of 443 patients with a donor to 588 patients without a donor, the data indicate that BCR-ABL-negative patients have a superior OS at five years (53% versus 45%, p=0.01) with allogeneic SCT compared to the no donor patients who were randomized to autologous SCT or chemotherapy. Of interest, this benefit was primarily seen in the standard risk patients (OS 62% for donor versus 52% for no donor patients, p=0.02), but not in high risk patients (OS 41% versus 35%, p=0.2). In both high risk and standard risk BCR-ABL-negative patients a clear

graft-versus-leukemia (GVL) effect was seen with significantly reduced relapse rates in donor patients (37% high risk and 24% standard risk for donor versus 63% high risk and 49% standard risk for no donor patients for high risk and standard risk patients, respectively (p value for both comparisons < 0.0005). The lack of difference in outcomes between donor and no donor patients in the high risk group were in part related to a high non-relapse mortality of 36% at two years (20% at two years for the standard risk patients)[5]. Patients who relapsed from first CR had an overall survival at 5 years of only 7%. Better outcomes were seen in younger patients and those whose first CR duration was > 2 years, but in these better risk groups the overall survival was still only 11-12%[6]. Factors predicting for a poorer overall and disease-free survival were older age, white blood cell count over 30 x 10^9/L for B lineage or over 100 x 10^9/L for T lineage, and B lineage patients had a poorer outcome than T lineage. Of interest, the achievement of a CR within four weeks did not appear to be an independent prognostic factor[7] . To build on our prior experience the chemotherapy backbone of the trial proposed here, E1910, will be based on the UKALLXII/E2993 chemotherapy regimen.

A study by Pulte et al. showed that outcomes in ALL worsen with increasing age[8], and this may, in part, be related to the fact that pediatric regimens have more intensive doses and schedules of chemotherapy than adult regimens. Adolescents and young adults are sometimes treated by pediatric hematologists and sometimes by adult hematologists, so it was appropriate to ask whether outcomes of adolescents and young adults (AYA) on pediatric regimens were superior to AYA treated on adult regimens. Multiple retrospective studies in the United States and Europe have now demonstrated that, in the majority of these comparisons, survival outcomes are improved in AYA who are treated on pediatric as opposed to adult regimens. This was first demonstrated in a comparison of data from the Cancer and Leukemia Group B (CALGB) and the Children's Cancer Group (CCG). A total of 321 AYA ages 16 to 20 were compared. Although the CR rates were identical at 90% between the two groups, the AYA in the CCG study had a 63% EFS and 67%OS at 7 years compared to the CALGB AYA where the 7-year EFS was only 34% and overall survival only 46% (p < 0.001)[9]. A puzzling finding from this study was that the EFS for the 16- to 17-year-olds on the CALGB study was similar to the same age group on the CCG study (55% vs. 64%, respectively, p=0.49). The inferior outcome for the CALGB patients was confined to the 18- to 20-year-olds whose EFS was only 29% as compared with 57% for the 18- to 20-year-old patients treated on the CCG studies (p=0.01). The CCG patients received intensive and earlier central nervous system prophylaxis, which resulted in a significantly lower incidence of isolated central nervous system relapses. Also the doses of non-myelosuppressive drugs such as corticosteroids, vincristine (VCR), and L-asparaginase were much higher in the CCG regimens compared with the CALGB regimens. This increased intensity of non-myelosuppressive drugs was especially seen in post-remission therapy[9]. The other retrospective studies have shown largely similar outcomes with improved survivals in AYA treated on pediatric regimens compared to AYA treated on adult regimens and also confirmed that the pediatric regimens contain higher doses of non-myelosuppressive drugs. The findings from these multiple studies are summarized in two recent publications[10,11]. Whether the improved outcomes seen with AYA treated on pediatric regimens are solely a result of the higher doses of

non-myelosuppressive drugs or whether they relate to other factors such as the greater experience of pediatric hematologists in caring for AYA with ALL compared with adult hematologists-oncologists or to stricter adherence to scheduled treatment regimens is unclear[12].

These studies have prompted the development of phase II trials utilizing pediatric-intense regimens in the young and middle-aged adults. The GRAALL-2003 trial was a phase II study where patients between the ages of 15 and 60 were eligible to receive a "pediatric-inspired therapy" that contained higher doses of L-asparaginase, VCR, and prednisone compared with the group's previous adult protocols. The EFS and OS were 55 and 60% with a median follow-up of 42 months, respectively. Age was an important factor in outcome. The authors identified a best age cutoff of 45 years with patients over this age having a chemotherapy-induced death rate of 23% as compared with 5% in younger patients who had EFS of 58% compared with 46% in the older patients ($p=0.03$)[13]. The authors did not specify if there was any difference in outcome by age within the group of patients aged 15 to 45 years. A study from Canada by Storring et al. treated 85 adults with BCR-ABL-negative ALL between the ages of 18 and 60 with a modified pediatric regimen that included weekly high doses of asparaginase for up to 30 weeks during intensification. At a median follow-up of 4 years, the estimated 5-year OS and relapse-free survival were 63% and 71%, respectively. Patients at or less than the age of 35 years had a 3-year OS of 83%, while patients over the age of 35 had an OS of 52%[14]. A trial reported by Ribera et al. in patients between the ages of 15 and 30 utilizing a pediatric-based protocol had an EFS and OS of 61% and 69% at 6 years with no difference in outcome noted between patients ages 15 to 18 and those 19 to 30 years of age. The hematologic toxicity was higher in the older group[15].

No randomized trials comparing pediatric-based protocols to standard adult protocols have been reported, but an innovative approach to attempt to prospectively compare these regimens is the CALGB 10403 protocol, which is treating adults with BCR-ABL-negative ALL up to the age of 40 years with a regimen that is taken from one arm of a CCG protocol. The CALGB 10403 study is a phase II study, but the results will be compared to the outcomes of patients treated on the designated arm of the CCG protocol. This will allow for a prospective comparison. In addition to the usual outcomes and toxicity measurements, particular attention will also be placed on whether patients and physicians were able to adhere to the dosing and scheduling requirements of the protocol. An interim analysis of the results of the C10403 trial compared to similar aged patients treated on prior CALGB trials has suggested a significant improvement in outcome with the pediatric-based regimen (personal communication, Wendy Stock, MD). Given these encouraging results, components of the C10403 trial and other pediatric regimens will be incorporated into the design of E1910 in an attempt to improve the chemotherapy backbone without excessively increasing toxicity.

However, these studies of pediatric-intensive regimens in adults indicate that while intensification of non-myelosuppressive chemotherapy improves outcomes, it is not well-tolerated by older adults and the ability to further intensify these regimens is limited. Furthermore, even with this incremental improvement, many patients will continue to relapse and die from their ALL. Alternative therapies are needed to improve the outcome for patients of older age. Addition of monoclonal

antibody therapy represents a potentially promising approach. To place the use of monoclonal antibody therapy in ALL in context, the role of MRD testing will be discussed next.

1.2 Minimal Residual Disease (MRD) Testing

The high rate of relapse seen in patients with adult ALL indicates that many patients have persistent residual disease despite achievement of a morphologic CR. The introduction of sensitive molecular techniques utilizing clonal immunoglobulin or T-cell receptor gene rearrangements has been effectively utilized to detect MRD. More than 10 years ago, it was demonstrated in pediatric ALL that the presence of residual disease at the end of induction chemotherapy or at later time points was a significant predictor of relapse that was independent of other risk factors[16]. The challenge of utilizing immunoglobulin or T-cell receptor gene rearrangement studies is that each patient's gene rearrangement is unique and must be characterized for each patient. An alternative is to take advantage of the increasing sophistication of flow cytometry to identify the distinct immunophenotypes in patients that allow detection of one leukemia cell amongst 10,000 normal cells[17]. In adult ALL, the German Multicenter Study Group for Adult ALL (GMALL) has demonstrated that patients who have a rapid decline in their MRD level within the first month of therapy had a 3-year relapse rate of 0%. Another subset of patients who had MRD detectable until week 16 of chemotherapy had a 3-year relapse rate of 94%. Patients in between these two groups had an intermediate risk of relapse of 47%[18]. Investigators in Italy, Poland and Spain have shown similar results with polymerase chain reaction (PCR) or flow cytometry techniques as indicated in the table below.[19-21]

AUTHOR	GROUP	METHOD	N	PROGNOSTIC MODEL	DFS
Bruggeman[18]	GMALL	PCR	105	$< 10^{-4}$ d11 + $< 10^{-4}$ d24	100%
				$> 10^{-4}$ d11 + $> 10^{-4}$ d24	6%
				All others	53%
Holowiecki[19]	PALG	Flow	115	$< 10^{-3}$ (4 weeks)	61%
				$> 10^{-3}$ (4 weeks)	17%
Bassan[20]	NILG	PCR	142	$< 10^{-4}$ wk16, $< 10^{-4}$ wk 22	72%
				All others	14%
Ribera[21]	PETHEMA	Flow	235	$< 10^{-3}$ (4 weeks), $< 5x10^{-4}$ (end consolidation)	54%
				$> 10^{-3}$ (4 weeks), $> 5x10^{-4}$ (end consolidation)	31%

A subset analysis of the MRC/ECOG trial patients who were MRD positive by immunoglobulin gene rearrangement studies after 2 months of induction chemotherapy had a relative risk of relapse that was 9-fold higher than the MRD-negative patients, and the 5-year relapse-free survival was 15% for those who were MRD-positive compared to 71% in the MRD-negative patients[22]. Thus, incorporation of MRD assessment is an important component of the management of pediatric and adult patients with ALL and plays an important role

in risk stratification. A recent review article has suggested that MRD should be "considered as a quantitative and objective extension of established endpoints of hematological remission and relapse" rather than a substitute for established risk factors[23]. Further advances in this field incorporating next generation sequencing also promise to bring greater sensitivity to the detection of MRD[24]. The adult cooperative groups in the United States have not yet developed a standardized assay for MRD assessment in adults with ALL that utilizes molecular or immunophenotypic techniques. However, given the labor intensity required to develop primers for individual patients and the equivalence of PCR and flow cytometry[25], flow cytometric approaches will be utilized for MRD assessment in this trial. The development and use of such an assay is an important component of this trial as discussed in the correlative science section of this concept proposal. Furthermore, the NCI has initiated a standardization effort for flow cytometric MRD assessment in ALL and the agreed upon antibody panel and procedures will be used by the ECOG-ACRIN laboratory in the MRD determination for this trial.

1.3 Monoclonal Antibody Therapy of Adult ALL

The classification of ALL by immunophenotype plays a key role in diagnosis and is playing an emerging role in the identification of MRD. CD20 is a B-lineage antigen that is expressed on both normal and malignant lymphocytes during all except the earliest and latest stages of B cell differentiation. It is expressed on B-lineage ALL in 40 to 50% of cases. CD20 antigen density (reflected by fluorescence intensity of antibody binding) and the percentage of CD20 expressing blasts are lowest in immature subtypes, such as CD10 negative Pro-B ALL, and in B-lineage ALL associated with the MLL/AF4 transcript. The prognostic importance of CD20 expression in newly diagnosed B-lineage ALL has been evaluated in both the pediatric and adult setting. In a Pediatric Oncology Group Study, CD20 expression and higher fluorescence intensity of CD20 antibody binding were associated with inferior EFS, independent of other known prognostic factors such as age and karyotype[26]. However, a study from St. Jude Children's Hospital suggested that CD20 expression was associated with slightly better outcomes[27]. These differences were attributed to treatment effects. At the MD Anderson Cancer Center, the prognostic significance of CD20 expression was analyzed in a group of 253 adult patients. Forty-seven percent of patients expressed CD20 on ≥ 20% of leukemic lymphoblasts. These patients had more thrombocytopenia, poorer performance status, and less lymphadenopathy than their CD20-negative counterparts. The CR rate was similar regardless of CD20 expression, but disease recurrence was higher in the CD20-positive group, which led to a significant decrease in remission duration and OS. In multivariate analysis, CD20 expression was an independent predictor of outcome. This detrimental effect of CD20 expression was particularly prominent in patients under the age of 60[28].

Rituximab, a chimeric IgG-1 anti-CD20 monoclonal antibody, induces antibody-dependent cell-mediated cytotoxicity, apoptosis and complement-mediated cytolysis[29]. Combining rituximab with frontline chemotherapy regimens has significantly improved outcomes for patients with non-Hodgkin lymphoma and Burkitt-type leukemia/lymphoma[30-32].

A recently published study combining rituximab with the hyperCVAD regimen in B-lineage ALL has been shown to be feasible and efficacious. Two hundred and

eighty-two adolescents and adults with de novo BCR-ABL negative B-lineage ALL were treated with hyperCVAD plus rituximab, and the results were compared to historical patients receiving hyperCVAD alone. The CR rate with rituximab plus hyperCVAD was 95% with 3-year rates of CR duration and OS of 60% and 50%. In patients under the age of 60, rates of CR duration and OS with the hyperCVAD and rituximab regimen compared with standard hyperCVAD alone were 70% vs. 38% ($p < 0.001\%$) and 75% vs. 47% ($p=0.003$), respectively at 3 years. Patients over the age of 60 with CD20-positive ALL did not benefit from rituximab plus hyperCVAD with rates of CR duration of 45% vs. 50% (p=NS) and OS 28% vs. 32% (p=NS). This was related in part to increased deaths in CR[33]. In a series of GMALL adult ALL patients between the ages of 15 and 55 years, 41% expressed CD20 on >20% lymphoblasts and these patients received rituximab 275 mg/m^2 day -1 before each induction course and before each of 6 consolidations for a total of 8 doses[34]. One hundred and seventeen patients received rituximab in addition to chemotherapy compared to 70 patients who received chemotherapy alone. In the standard-risk patients, CR and early death rates were similar between the two groups. However, the course of MRD differed significantly, in that there was a faster decrease in MRD in those who did versus those who did not receive rituximab, with molecular CR (MRD < 10^{-4}) reached at day 21 in 60% vs. 19% of patients, respectively. The probability of continuous CR at 3 years was 64% vs. 48%, respectively ($p=0.009$) and for OS 75% with rituximab vs. 54% without at 3 years. For high-risk patients, the OS at 3 years was 54% with rituximab and 32% without. Of the high-risk patients, 66% went on to BMT in first remission, and their OS was superior if they received rituximab pretransplant at 75% vs. 40% for those who were transplanted without receiving prior rituximab. This difference in outcome was attributable to fewer relapses in those who received rituximab[34]. The results of these studies, warrant further exploration of monoclonal-directed antibody therapy in ALL. Randomized trials of chemotherapy with rituximab compared to chemotherapy alone are awaited to determine if these retrospective results are confirmed.

A novel approach to increase the efficacy of monoclonal antibody therapy is to utilize them to harness the tremendous cytotoxic potential of T-cells using a bi-specific T-cell engaging (BiTE) antibody construct. In the case of blinatumomab, the variable regions of 2 parental murine antibodies are connected via a short linker sequence. Blinatumomab combines the variable regions of an anti-CD19 antibody directed against B-cells and an anti-CD3 antibody directed against T-cells. These BiTE antibodies physically link T-cells and in this case, malignant (and normal) B-cells and also trigger the signaling cascade of the T-cell receptor complex by binding to the CD3 portion of the receptor. This triggers polyclonal T-cell recruitment with subsequent activation that occurs only if the second portion of the BiTE antibody is bound to its target antigen on the B- cell surface. Single binding of the BiTE antibody to T-cells does not cause T-cell activation[35-36].

Blinatumomab has been utilized in the treatment of patients with non-Hodgkin lymphoma in a phase I trial utilizing doses of 60 µg/m^2 per day given by continuous intravenous infusion for 4 to 8 weeks (NCT00274742). A recent report on the results of 12 patients with indolent follicular or mantle cell lymphoma demonstrated objective responses in 11 of 12 patients with 7 partial responses (PR) and 4 CR. The median response duration was 12 months with 6 of 11 responses still ongoing at the time of the report. A single non-responding patient experienced a reversible neurological adverse event and was discontinued from

treatment early. Four patients had neurologic symptoms which were all reversible, and one patient had a port infection[37]. An update of the trial reported in abstract form of 14 patients with mainly follicular and mantle cell subtypes treated at 60 μ/m^2/day demonstrated nine CR and four PR in 13 evaluable patients. As of February, 2010 response duration was up to 27+ months. Eight of 13 responses were on-going after a median follow-up of 13 months. The single non-evaluable patient experienced a fully reversible, neurological adverse event leading to early discontinuation of therapy. Of the 13 responders, five had adverse events that were all fully reversible and consisted of one port infection and four neurologic events. These neurologic events were predicted by low peripheral blood B:T cell ratios. Implementation of a lower initial starting dose of 5 and/or 15 μ/m^2/day for 1-2 weeks followed by 60 μ/m^2/day significantly lowered the risk of these adverse events[38]. An amendment to this study allowed the enrollment of patients with relapsed diffuse large B cell lymphoma. Two cohorts of six patients each were enrolled and they differed solely by the dose and schedule of corticosteroid pre-medication administered prior to blinatumomab to lessen adverse effects. Five of nine evaluable patients (56%) showed objective clinical responses (4 CR/CRu; 1PR).[39]

Blinatumomab has also been tested in B-ALL patients but at a lower dose of 15 μg/m^2 per day by continuous infusion for 4 weeks (NCT00560794). The rationale for the lower dose is that in pilot studies, bone marrow clearance was seen at the 15 μg/m^2 per day dose. Patients in complete hematologic remission with either persistent or recurrent MRD at any time after initial consolidation of frontline therapy were eligible. Of 19 patients treated, 16 were evaluable for response; 13 of 16 went into molecular CR after 1 cycle of blinatumomab. Three patients had stable MRD. Ten of the 13 responding patients had never achieved a molecular CR before blinatumomab treatment despite multiple treatment cycles including tyrosine kinase inhibitors in the case of BCR-ABL-positive ALL. Two patients with molecular CR had an extra-medullary relapse, one in the testis and one in the CSF. The most common adverse events were lymphopenia, pyrexia, leukopenia, and hypogammaglobulinemia. Overall, the treatment was well tolerated[40]. A report of 21 patients enrolled in the trial (16 BCR-ABL-negative; 2 patients with MLL-AF4; 5 pts with BCR-ABL-positive ALL) demonstrated that 16 of 20 evaluable patients became MRD-negative. Of these, 13 had never before achieved MRD negativity on chemotherapy. All 16 patients (13/15 BCR-ABL-negative and 3/5 BCR-ABL-positive) became MRD negative after the first cycle of blinatumomab. Nine patients were enrolled with an MRD load > 10^{-2} prior to study treatment and all reached a complete MRD response. Overall relapse-free survival was 78% at the time of the report with a median follow-up of 405 days. Eight patients underwent allogeneic transplant (6 responders and 2 non-responders) and 8 are alive in hematologic remission with a median follow-up of 434 days[41]. The most recent update of this trial shows that with a median follow-up of 33 months, the hematological relapse-free survival of the entire evaluable cohort of 20 patients is 61% by Kaplan-Meier estimation. In a sub-group of six BCR-ABL-negative patients who received no further therapy after blinatumomab, four remain in hematologic and molecular remission[42].

Analysis of a phase II study in adult patients with ALL in hematologic relapse or refractory disease determined that the CR or CRh (CR with incomplete hematologic recovery) rate was 68% (17 of 25 patients) in patients treated at the optimal schedule of 5 μg/m^2/day for the first week followed by 15 μg/m^2/day for

the subsequent three weeks (NCT01209286). All responders achieved a negative MRD status (level < 10^{-4}) within the first two cycles of therapy. Six patients proceeded to allogeneic transplant after blinatumomab therapy and one of them had a CD19 negative medullary relapse post-transplant. Of the 11 patients not transplanted, five have relapsed-two were CD19 negative (one medullary and one extra-medullary) and three were CD19 positive (one medullary and two extra-medullary). Median response duration is 7.1 months with the median survival not yet reached and median follow-up time is 11.4 months. The most significant toxicities in 25 evaluable patients were CNS events (seizures and disorientation) in five and DIC/cytokine release syndrome in two patients.[43,44]. Three pediatric patients in hematologic relapse after allogeneic BMT were treated with blinatumomab and all achieved a molecular CR after four to six weeks of therapy. No graft-versus-host disease developed[45].

Globally, 20 deaths have been reported in patients on blinatumomab trials. Five of the 20 (1 bacterial sepsis, 1 pneumocystis jiroveci pneumonia, 1 invasive fungal infection, 1 cardiac and respiratory failure, 1 respiratory failure) were considered by the investigator to be possibly related to blinatumomab (Investigator's Brochure, edition 14.2).

Blinatumomab represents a promising therapy in B-ALL and further trials are planned with larger patient numbers to better understand its benefit and efficacy, including an international trial for relapsed/refractory patients that is currently on-going.

1.4 Blinatumomab Dosing: Pharmacokinetic justification for fixed dosing versus dosing based on body surface area

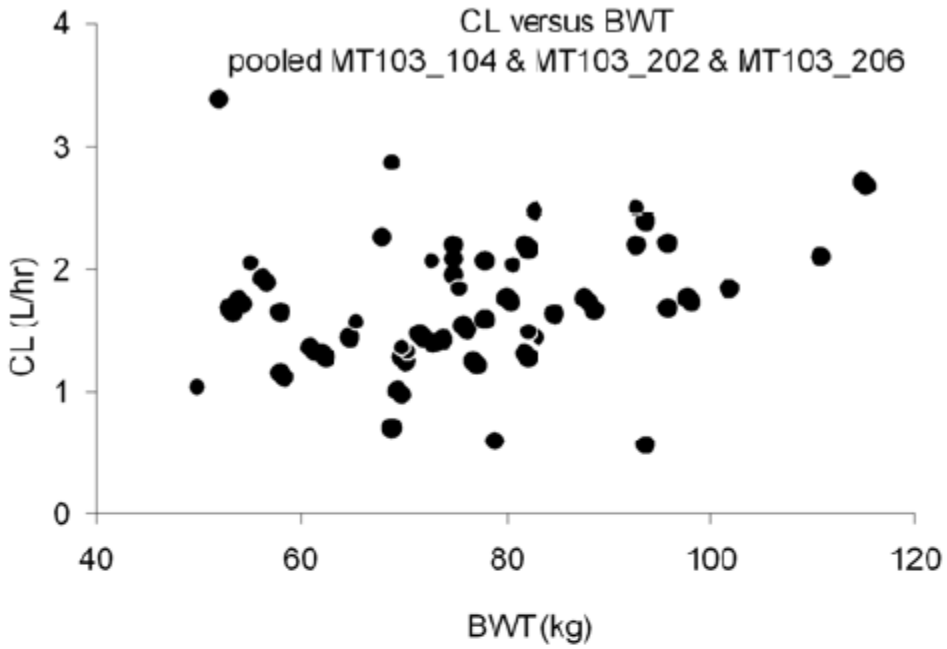
The use of a fixed dose is expected to provide better compliance and less risk of medical errors in dose calculation. Therefore, Amgen analyzed the available exposure data from BSA-normalized doses from clinical trials to explore the effect of BSA and body weight (BWT) on clearance and to evaluate the variability in clearance under different dosing approaches i.e. fixed doses and BSA or BWT normalized-dosing. Available data as of May 20, 2011 (trials: MT103-104, MT103-202, and MT103-206) were pooled. The average Css through different cycles in each individual patient were considered. The clearance (CL =Ro/Css, where Ro is the dosing rate) was calculated and then normalized to BSA or BWT. The variability (CV%) in CL, CL/BSA, and CL/BWT was computed and compared. The CV% was also calculated for Css normalized to absolute dose, dose/kg or dose/m^2 and compared.

Figure 1 (a, b) shows no remarkable effect of either BWT or BSA on the clearance of blinatumomab. The results in Table 1, indicate that normalizing to BSA does not reduce inter-patient variability in systemic exposure which supports the feasibility of administering blinatumomab using a fixed dose regimen, as an alternative to the currently used BSA normalized dosing. Population PK analysis is foreseen to confirm these findings with more data becoming available.

The average BSA in the trials population was 1.9 m^2 (MT103-104, MT103-206 and MT103-202 clinical trials). Using this conversion factor a dose of 15 mcg /m^2 blinatumomab is equivalent to 28.5 mcg and a dose of 5 mcg /m^2 is equivalent to 9.5 mcg. Therefore fixed doses of 9 mcg /day and 28 mcg /day (instead of 5 mcg

/m^2/day and 15 mcg /m^2/day, respectively) are proposed to be used in future trials including this one.

(a)



(b)

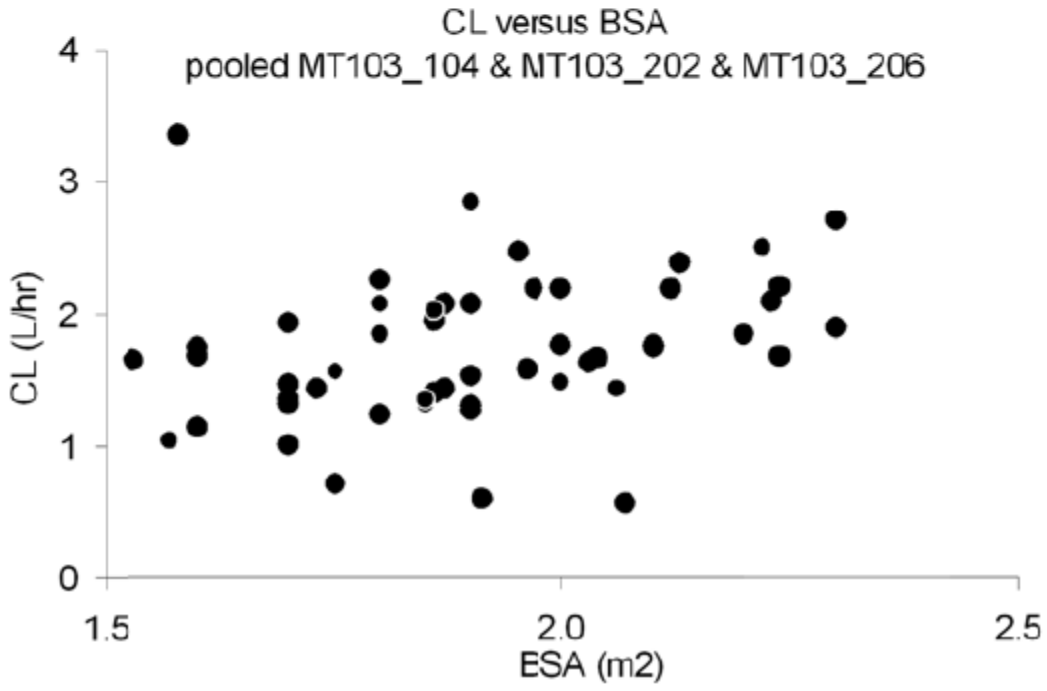


Figure 1(a) Relationship between CL and BWT, (b) Relationship between CL and BSA.

Table 1: Mean clearance values and dose normalized Css values*

	CL (L/hr)	CL/BWT (L/hr/kg)	CL/BSA (L/hr/m^2)	Css/ Absolute Dose (pg/mL/µg/day)	Css/ BSA-Dose (pg/mL/µg/m^2/day)	Css/ BWT-Dose (pg/mL/µg/kg/day)
Mean	1.738	0.023	0.920	27.048	50.187	2042.6
SD	0.543	0.009	0.297	10.99	20.22	913.1
CV%	31.24	38.5	32.25	40.63	40.28	44.7

*Data Source: 54 patients pooled from clinical studies MT103-104, MT 103-202 and MT 103-206 with and without normalization to body size (BWT, BSA), together with variability parameters.

In summary, dose normalization to BSA does not reduce inter-patient variability in systemic exposure which supports the feasibility of administering blinatumomab using a fixed dose regimen, as a potential alternative to the currently used BSA normalized dosing. Administration of blinatumomab as a fixed dose regimen is expected to lead to better compliance, and less risk of medical errors.

In conclusion, the data from the clinical trials MT103-104, MT103-202, and MT103-206, serve as basis for the treatment plan selected for this trial. Step dosing was originally developed to prevent cytokine release syndrome in patients with high tumor burden. Currently for patients in remission "flat" dosing without a step up (28mcg/day) is utilized. Previous studies[41,42] and an on-going clinical trial (MT103-203) have shown that step dosing is not necessary for patients in hematologic remission. It is therefore recommended that "flat" dosing without a step up be used to be consistent with current ongoing studies. Thus, the selected dose and regimen in this E1910 trial will consist of a dose of 28 mcg/day from the first day of the first cycle and for all the following cycles to achieve a high degree of efficacy.

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1.5 Summary

The poor prognosis of older adults with B ALL and their inability to tolerate intensive chemotherapy suitable for children and younger adults necessitates the incorporation of novel agents into the therapeutic regimens of these patients. The encouraging results of therapy with blinatumomab in converting patients who are MRD positive to MRD negative status and the acceptable toxicity profile seen with this bi-specific antibody suggest that it has the potential to improve survival and quality of life of older adults with B ALL. It will also be an important proof of biologic principle that BiTE therapy has the potential to improve outcomes in this challenging patient population. This trial will utilize the chemotherapy program from the UKALLXII/E2993 trial with dosing modifications based on the improved outcomes that are emerging from the completed C10403 AYA trial. Data from the GMALL group suggests that pegaspargase is less well-tolerated in older adults and therefore, will be omitted in patients 55 and older in induction (personal communication, N.Goekbuget)[46]. These patients also tolerate high-dose corticosteroid doses less well than younger adults and will, therefore, receive shorter courses of corticosteroids in the protocol.

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A recently published trial of blinatumomab for adults with B-cell precursor ALL in hematologic complete remission with positive MRD results ($\geq 10^{-3}$) demonstrated that 82 of 103 patients (80%) achieved a complete MRD response after one cycle of blinatumomab with significantly improved survival compared to patients who did not achieve a complete MRD response.[79] Based on this data on March 29, 2018, the U.S. Food and Drug Administration granted accelerated approval to blinatumomab to treat adults and children with B-cell precursor ALL who are in remission but still MRD positive. On E1910 it had already been observed prior to this approval that patients who were MRD positive at the time of Step 3 randomization were being taken off-study either prior to randomization or after randomization if they were not randomized to blinatuomomab. Therefore, the protocol is being amended to assign MRD positive patients at step 3 to Arm C to receive 2 cycles of blinatumomab and then continue on protocol to either go to allogeneic BMT or continue consolidation chemotherapy and subsequent blinatumomab and maintenance therapy.

2. Objectives

2.1 Primary Objectives

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2.1.1 To compare the overall survival (OS) of blinatumomab in conjunction with chemotherapy to chemotherapy alone in patients with BCR-ABL-negative B cell precursor ALL who are MRD negative after induction and intensification chemotherapy, based on multiparameter flow cytometric (MFC) assessment of residual blasts.

2.2 Secondary Objectives

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2.2.1 To compare the relapse-free survival (RFS) of blinatumomab in conjunction with chemotherapy to chemotherapy alone in MRD negative patients after induction and intensification chemotherapy.

2.2.2 To compare the OS and RFS of those patients who are MRD+ at step 3 randomization/ registration and then convert to MRD- after 2 cycles of blinatumomab to those patients who are MRD- at randomization and remain MRD- after 2 cycles of blinatumomab or consolidation chemotherapy.

2.2.3 To assess the toxicities of blinatumomab in this patient population

2.2.4 To assess the toxicities of the modified E2993 chemotherapy regimen in this patient population.

2.2.5 To describe the outcome of patients who proceed to allogeneic blood or marrow transplant after treatment with or without blinatumomab.

2.3 Laboratory Objectives

2.3.1 To determine differences in MRD kinetics among patients with the BCR/ABL1-like B-lineage ALL, and to compare the OS (and RFS) of patients with BCR-ABL-like phenotype with those without BCR-ABL-like phenotype.

2.3.2 To evaluate the incidence of anti-blinatumomab antibody formation.

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3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: This study involves pre-registration (see Section 4). Bone marrow and peripheral blood specimens must be submitted for centralized immunophenotyping.

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3.1 Pre-Registration

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_____ Diagnostic bone marrow and/or peripheral blood specimens **must be submitted** for immunophenotyping and selected molecular testing, and the establishment of BCR/ABL status. Testing will be performed by the ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL) and reported to the institution.

NOTE: IT IS ESSENTIAL THAT A SAMPLE CONTAINING SUFFICIENT BLAST CELLS BE SUBMITTED TO THE ECOG-ACRIN LTRL AT BASELINE SO THAT SUBSEQUENT BONE MARROW ASSESSMENTS OF MRD CAN BE DONE. IN ADDITION TO ALLOWING THE LTRL TO CONFIRM ELIGIBILITY BASED ON BLAST CELL IMMUNOPHENOTYPE AND BCR/ABL STATUS, IT IS ALSO IMPERATIVE THAT AN ADEQUATE NUMBER OF BLASTS BE BANKED FOR ANALYSIS BY DRS MULLIGHAN/WILLMAN. WITHOUT ADEQUATE BASELINE SAMPLES, PATIENTS WILL NOT BE ABLE TO BE TREATED AND RANDOMIZED ON THIS PROTOCOL. IF A BONE MARROW ASPIRATE IS NOT AVAILABLE FOR LTRL SUBMISSION AT BASELINE, IT IS IMPERATIVE THAT DR PAIETTA FROM THE LTRL IS CALLED TO DISCUSS THE PERIPHERAL BLOOD WBC AND BLAST COUNT BEFORE BLOOD ONLY IS SUBMITTED.

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NOTE: Hydroxyurea can be given for up to 5 days prior to initiation of protocol therapy for control of leukocyte count and/or other symptoms or signs. Corticosteroids can be given after pre-registration to the protocol and submission of baseline marrow and blood samples for control of leukocyte count and/or other symptoms or signs prior to

initiation of protocol therapy if needed. If corticosteroids are given prior to pre-registration, contact the study chair as the patient may still be eligible to participate.

3.2 Induction Eligibility Criteria – Step 1

Rev. 7/14 _____3.2.1 Age ≥ 30 years and ≤ 70 years.

New diagnosis of B lineage ALL must be made upon bone marrow or peripheral blood immunophenotyping. Cases with myeloid antigen expression, but unequivocal lymphoid immunophenotype, are eligible.

_____ 3.2.2 Mature B ALL (Burkitt's-like leukemia) is excluded from enrollment in this trial.

Rev. 2/18 Pre-study bone marrow biopsy and aspirate must be completed ≤ 1 week prior to registration.

_____ 3.2.3 Negativity for the Philadelphia chromosome must be established by conventional cytogenetics, FISH and/or PCR. Patients who are negative for the Philadelphia chromosome by conventional cytogenetics must have FISH or PCR performed for BCR/ABL to exclude occult translocations.

_____ 3.2.4 Cytogenetic analysis must be performed from diagnostic bone marrow (preferred) or if adequate number of circulating blasts from peripheral blood. FISH testing for common B-lineage ALL abnormalities including t(9;22) (*BCR/ABL1)*, t(12;21) (*ETV6/RUNX1)*, t(1;19) (*PBX1/TCF3),* +4,+10,+17, (Cen4/Cen10/Cen17), t(11q23;var), *(MLL)*, del(9p) (*CDKN2A*/Cen9), and t(14;var) (*IGH* is encouraged. If there are few or no circulating blasts and an adequate marrow sample cannot be obtained for cytogenetic analysis, the patient may still enroll on the trial.

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_____ 3.2.5 Patient must not have a concurrent active malignancy for which they are receiving treatment.

Rev. 6/15 _____ 3.2.6 Have lab values obtained ≤ 48 hours prior to registration. Serum direct bilirubin < 2 mg/dl **or** serum total bilirubin ≤ 3, and serum creatinine < 2 mg/dl.

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Serum direct bilirubin: _____ Serum creatinine: _____

Serum total bilirubin: _____

Date of tests: _____

NOTE: The above stipulation for normal hepatic function does not apply if liver dysfunction is due to leukemia infiltration.

_____ 3.2.7 Patient should be HLA typed (A, B, C, DR and DQ) during induction therapy phase or a written explanation for not undergoing HLA typing on the flow sheet.

_____ 3.2.8 Patient must not have intercurrent organ damage or medical problems that will jeopardize the outcome of therapy (i.e., psychiatric disorder, drug abuse, pregnancy).

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_____ 3.2.9 Patients with known HIV infection are eligible If they meet all of the following criteria:

3.2.9.1 No history of AIDS-related complications other than a history of low CD4+ T-cell count (< 200/mm3) prior to initiation of combination antiretroviral therapy. On study CD4+ T-cell count may not be informative due to leukemia and should not be used as an exclusion criterion if low.

3.2.9.2 Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the leukemia.

3.2.9.3 Patient must have serum HIV viral load of < 200 copies/mm^3.

3.2.9.4 Patient must be on combination antiretroviral therapy with minimal pharmacokinetic interactions with study therapy and minimal overlapping clinical toxicity with protocol therapy.

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3.2.9.5 Patient must not be receiving protease inhibitors or once daily formulations containing cobicistat, stavudine, or on regimens containing stauvidine or zidovudine.

3.2.9.6 It is recommended to utilize a regimen of the integrase inhibitor, dolutegravir, combined with either disoproxil fumarate/emtricitabine or dolutegravir combined with tenofovir alafenamide/emtricitabine.

_____ 3.2.10 Patient must not have an antecedent hematologic disorder.

_____ 3.2.11 Patient must have no history of recent myocardial infarction (within three months), uncontrolled congestive heart failure, or uncontrolled cardiac arrhythmia.

_____ 3.2.12 Patient must not have a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or other significant CNS abnormalities.

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_____ 3.2.13 Patient must have a normal cardiac ejection fraction by pretreatment MUGA or echocardiogram within 4 weeks prior to registration (resting ejection fraction ≥ 40% or ≥ 5% increase with exercise), shortening fraction by echocardiogram ≥ 24%, or to within the normal range of values for the institution.

_____ 3.2.14 Patient must not have an active uncontrolled infection.

_____ 3.2.15 Women must not be pregnant or breast-feeding due to administration of teratogenic chemotherapy and must not become pregnant or breastfeed during protocol therapy and for at least 3 months after protocol therapy. Woman of childbrearing potential must abstain from sexual activity or be willing to use 2 highly effective forms of contraception throughout protocol therapy and for at least an additional 3 months after the last dose of protocol-specified therapy.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.2.16 Men who have a female partner of childbearing potential must be willing to use 2 highly effective forms of contraception throughout protocol therapy and for at least an additional 3 months after the last dose of protocol-specified therapy.

Men who have a pregnant partner must be willing to use a condom during sexual activity throughout protocol therapy and for 3 months after the last dose of protocol-specified therapy.

_____ 3.2.17 ECOG performance score 0-3.

_____ 3.2.18 Patient must have given written informed consent.

3.3 Post-Induction Therapy Eligibility Criteria (prior to Intensification – Step 2)

_____ 3.3.1 ECOG performance status 0-2.

_____ 3.3.2 Patients must have achieved a CR or CRi as defined in Section 6.

_____ 3.3.3 Patients who have achieved a CR or CRi must have maintained peripheral blood evidence of a CR or CRi as defined in Section 6.

_____ 3.3.4 Patient must be CNS (CSF) negative for leukemia.

_____ 3.3.5 Patients must have resolved any serious infectious complications related to induction.

_____ 3.3.6 Any significant medical complications related to induction must have resolved.

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_____ 3.3.7 Have lab values obtained ≤ 48 hours prior to registration. Patients must have serum creatinine ≤ 2.0 mg/dl.

Serum creatinine: _____

Date of tests: _____

Serum direct bilirubin < 2 mg/dL **or** serum total bilirubin ≤ 3, and AST and ALT < 3x upper limit of normal (ULN).

Serum direct or total bilirubin:_____

AST: _____

ALT: _____

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3.4 Randomization or Assignment to Blinatumomab or No Blinatumomab – Step 3

_____ 3.4.1 Patients must have an ECOG performance status of 0-2.

_____ 3.4.2 Patients must have maintained peripheral blood evidence of a remission as defined in Section 6 and must have a CR or CRi, confirmed on restaging BM aspirate and biopsy.

_____ 3.4.3 Patients must have resolved any serious infectious complications related to therapy.

_____ 3.4.4 Any significant medical complications related to therapy must have resolved.

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_____ 3.4.5 Patients must have a direct or total bilirubin < 1.5xULN (unless related to Gilbert's or Meulengracht's syndrome, and a serum creatinine < 1.5 x ULN. The values must be obtained within 48 hours prior to randomization.

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_____ 3.4.6 **Bone marrow aspirates must be submitted as outlined in Section 10 for centralized minimal residual disease (MRD) assessment performed by the ECOG-ACRIN Leukemia Translational Research Laboratory.**

Rev. 3/15

_____ 3.4.7 **MRD results will be reported to the submitting institution.**

NOTE: FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

NOTE: Failure to submit bone marrow aspirates will result in a major violation at the time of an audit.

3.5 Criteria for Allogeneic Transplantation

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_____ 3.5.1 A suitable donor must be identified. There are no restrictions on donor type and can include a matched sibling, a matched or mismatched unrelated donor, a family haplotype matched donor or a cord blood donor (single or double).

_____ 3.5.2 Patients should meet the eligibility criteria in Section 3.4.

_____ 3.5.3 Patients must be considered reliable enough to comply with the medication regimen and follow-up, and have social support necessary to allow this compliance.

3.6 Criteria for Maintenance Therapy – Step 4

_____ 3.6.1 Patients must have an ECOG performance status of 0 -3.

Rev. 8/17

_____ 3.6.2 Patients must have maintained peripheral blood evidence of a remission as defined in Section 6 and must have a CR or CRi, confirmed on restaging BM aspirate and biopsy.

_____ 3.6.3 Patients must have resolved any serious infectious complications related to therapy.

_____ 3.6.4 Any significant medical complications related to therapy must have resolved.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration Procedures

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CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

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Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

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CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

This study commences with a single induction arm.

At the time of registration, investigators should declare whether, to the best of their knowledge, the patient is a potential candidate for allogeneic hematopoietic cell transplantation (HCT) or not.

All patients who meet CR or CRi criteria in Section 6 at the end of induction therapy receive a single cycle of intensification therapy and are either *randomized to*:

2 cycles of blinatumomab followed by allogeneic HCT or consolidation/maintenance chemotherapy or proceed directly to allogeneic HCT or consolidation/maintenance chemotherapy.

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Patients who do not meet CR or CRi criteria in Section 6 at the end of induction therapy will go off-study.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office.

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For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E1910** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E1910**
- Click on the LPO Documents, select the Site Registration documents link, and download and complete the forms provided

Requirements for E1910 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance

Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

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Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

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Required Protocol Specific Regulatory Documents

Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

A. CTSU IRB Certification Form.
Or
B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

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Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab

- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within three working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

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Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following information will be requested

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4.1 Pre-Registration

NOTE: Patients who are only pre-registered must not begin treatment. Treatment should start within three working days after registration.

To proceed to registration, patients must have centralized immunophenotyping performed by the ECOG-ACRIN Leukemia Translational Research Laboratory.

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.2.2 Investigator's name (NCI number)

4.1.2.3 Cooperative Group Credit

4.1.2.4 Credit Investigator

4.1.2.5 Protocol specific contact information

4.1.3 Patient Identification

4.1.3.1 Patient's initials (first and last)

4.1.3.2 Patient's Hospital ID and/or Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.3.3.7 Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

Rev. 8/17

NOTE: During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate, defined as 2 induction cycles worth of methotrexate, may not consent patients to the study.

Rev. 2/18

NOTE: During a shortage of sodium bicarbonate, institutions without a sufficient supply of sodium bicarbonate, defined as a one month supply, may not consent patients to the study.

Rev. 4/12, 6/16

4.1.6 Bone marrow and/or peripheral blood specimens **must be submitted** at pre-registration for centralized immunophenotyping.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston. However the ECOG-ACRIN Leukemia Translational Research Laboratory

(LTRL) requires institutions to submit a copy of the E1910 consent and a copy of the HIPAA Authorization form.

Rev. 3/15

NOTE: FACT (Foundation for the Accreditation of Cellular Therapy) credentialing certificate must be submitted to the CTSU Patient Registrar at 1-888-691-8039 at the time the patient elects to proceed to BMT.

4.2 Registration to Induction Arm A - Step 1

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.2.5 Classification

4.2.5.1 Intent to receive an allogeneic SCT or not

4.2.6 Additional Requirements

4.2.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

Rev. 8/17

NOTE: During a shortage of preservative-free methotrexate, institutions without a sufficient

supply of preservative-free methotrexate, defined as 2 induction cycles worth of methotrexate, may not consent patients to the study.

NOTE: During a shortage of sodium bicarbonate, institutions without a sufficient supply of sodium bicarbonate, defined as a one month supply, may not consent patients to the study.

4.2.6.2 Biological samples are to be submitted for defined laboratory research studies and/or future undefined research as outlined in Section 10.

Rev. 2/18
Rev. Add15

4.2.6.3 Data collection for this study will be done exclusively through Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via Medidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at

www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.2.6.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E1910 Forms Completion Guidelines.

4.3 Register to Post-Induction Therapy - Intensification - Step 2- Arm B

All patients meeting CR or CRi criteria in Sections 6.1 and 6.2 will register for post-induction therapy.

4.3.1 Protocol Number

4.3.2 Investigator Identification

4.3.2.1 Institution and affiliate name (Institution CTEP ID)

4.3.2.2 Investigator's name (NCI number)

4.3.2.3 Cooperative Group Credit

4.3.2.4 Credit Investigator

4.3.2.5 Protocol specific contact information

4.3.3 Patient Identification

4.3.3.1 Patient's initials (first and last)

4.3.3.2 Patient's Hospital ID and/or Social Security number

4.3.3.3 Patient demographics

4.3.3.3.1 Gender

4.3.3.3.2 Birth date

4.3.3.3.3 Race

4.3.3.3.4 Ethnicity

4.3.3.3.5 Nine-digit ZIP code

4.3.3.3.6 Method of payment

4.3.3.3.7 Country of residence

4.3.4 Additional Requirements

4.3.4.1 Biological samples are to be submitted for defined laboratory research studies and/or future undefined research as outlined in Section 10.

4.3.5 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E1910 Forms Completion Guidelines.

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Rev. 8/17

4.4 Randomization or Assignment to Blinatumomab or No Blinatumomab Step 3 (Arms C and D)

4.4.1 Protocol Number

4.4.2 Investigator Identification

4.4.2.1 Institution and affiliate name (Institution CTEP ID)

4.4.2.2 Investigator's name (NCI number)

4.4.2.3 Cooperative Group Credit

4.4.2.4 Credit Investigator

4.4.2.5 Protocol specific contact information

4.4.3 Patient Identification

4.4.3.1 Patient's initials (first and last)

4.4.3.2 Patient's Hospital ID and/or Social Security number

4.4.3.3 Patient demographics

4.4.3.3.1 Gender

4.4.3.3.2 Birth date

4.4.3.3.3 Race

4.4.3.3.4 Ethnicity

4.4.3.3.5 Nine-digit ZIP code

4.4.3.3.6 Method of payment

4.4.3.3.7 Country of residence

4.4.4 Stratification

Rev. 7/14

4.4.4.1 Age: < 55 years vs. age ≥ 55 years.

4.4.4.2 MRD status post intensification: Positive vs. Negative

4.4.4.3 CD20 status at study entry: Presence of distinct blast cell population of CD20 staining cells vs. absence of distinct blast cell population of CD20 staining cells

4.4.4.4 Rituximab use: Whether patient received or plans to receive rituximab

4.4.4.5 Whether patient intends to receive HSCT or not.

4.4.5 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E1910 Forms Completion Guidelines.

4.4.6 Additional Requirements

4.4.6.1 Bone marrow samples are required to be submitted for defined laboratory research studies as indicated in Section 10.

NOTE: FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

Rev. 7/14

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

Rev. 3/15

MRD results will be reported to the submitting institution.

4.4.6.2 Biological samples are to be submitted for defined laboratory research studies and/or future undefined research as outlined in Section 10.

4.5 Register to Maintenance Therapy – Step 4

4.5.1 Protocol Number

4.5.2 Investigator Identification

4.5.2.1 Institution and affiliate name (Institution CTEP ID)

4.5.2.2 Investigator's name (NCI number)

4.5.2.3 Cooperative Group Credit

4.5.2.4 Credit Investigator

4.5.2.5 Protocol specific contact information

4.5.3 Patient Identification

4.5.3.1 Patient's initials (first and last)

4.5.3.2 Patient's Hospital ID and/or Social Security number

4.5.3.3 Patient demographics

4.5.3.3.1 Gender

4.5.3.3.2 Birth date

4.5.3.3.3 Race

4.5.3.3.4 Ethnicity

4.5.3.3.5 Nine-digit ZIP code

4.5.3.3.6 Method of payment

4.5.3.3.7 Country of residence

4.5.4 Additional Requirements

4.5.4.1 Biological samples are to be submitted for defined laboratory research studies and/or future undefined research as outlined in Section 10.

4.5.5 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E1910 Forms Completion Guidelines.

5. Treatment Plan

Rev. Add14

5.1 Overall Study Design

NOTE: Chemotherapy may be given +/- 1 day from the scheduled day as outlined throughout Section 5

The study commences with a single induction arm that is administered in 2 cycles. Patients who achieve CR or CRi after induction will undergo intensification with high-dose methotrexate and then be randomized to receive or not receive two cycles of blinatumomab followed by allogeneic SCT or consolidation/maintenance therapy. Patients initially randomized to blinatumomab will receive 2 additional cycles of blinatumomab in consolidation for a total of 4 cycles of blinatumomab.

Rev. 3/15

Hydroxyurea can be given for up to 5 days prior to initiation of protocol therapy for control of leukocyte count and/or other symptoms or signs. Corticosteroids

Rev.6/16, 2/18

can be given after pre-registration to the protocol and submission of baseline marrow and blood samples for control of leukocyte count and/or other symptoms or signs prior to initiation of protocol therapy if needed. If corticosteroids are given prior to pre-registration, contact the study chair as the patient may still be eligible to participate.

Rev. 6/16

Patients may receive the Day 1 dose of intrathecal cytarabine prior to study registration (see Sections 5.2.1.4 and 5.2.2.1). If administered prior to study registration, systemic chemotherapy must begin within 72 hours of this intrathecal therapy.

Investigators must now declare their intention regarding allogeneic transplant for their patient as part of registration to step 3 as per Section 4.2.5.1. The intent is for patient to receive/not receive transplant regardless of blinatumomab randomization. All patients who are considered to be possible allogeneic SCT candidates must be HLA typed as soon as possible, preferably in Cycle 1 of induction, to prevent delays in proceeding to transplant.

The following options for donors should be explored:

1. The availability of a matched sibling donor.
2. The availability of a matched or mismatched unrelated donor (MUD or MMUD).
3. The availability of single or double cord blood unit(s).
4. The availability of a related haplotype match.

Rev. 3/15

NOTE: MRD assessments will be performed periodically during the course of treatment on this protocol as noted in Section 7 of the protocol.

FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT

SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

Rev. 7/14

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

5.2 Induction Therapy - Arm A

5.2.1 Initial Considerations

5.2.1.1 All patients are begun on Allopurinol at least 300 mg/day orally between days 1 and 22, inclusive. Reversible abnormalities of renal or metabolic function should be treated aggressively and corrected prior to induction. Provide appropriate and aggressive hydration as the situation warrants maintaining good urine output. Patients at high risk for tumor lysis syndrome can be considered for rasburicase therapy, 0.1 to 0.2 mg/kg/day IV over 30 minutes for 1-3 days or up to five days (or a flat dose of 3 or 6 mg daily) in addition to oral allopurinol depending on uric acid levels and the clinical status of the patient.

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Rev. 3/15

NOTE: Rasburicase is contraindicated in patient with G6PD deficiency with or without chronic non-spherocytic hemolytic anemia (CNSHA). Patients of Asian, African and Mediterranean ancestry should be tested for G6PD deficiency prior to starting rasburicase.

5.2.1.2 Immediate measures to diagnose and begin treatment of infections should be instituted prior to induction therapy.

5.2.1.3 Pre-medications including corticosteroids to prevent chemotherapy toxicities are permitted as per institutional standards.

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Rev. 6/16

5.2.1.4 Spinal Fluid Examination

- Regardless of spinal fluid sugar or protein concentrations or cell count, a concentrated properly stained sediment should be examined (preferably by cytospin technique) for the presence of blast forms. This spinal fluid exam can be done prior to study registration or on day 1 of therapy with administration of intrathecal cytarabine (see Section 5.2.2.1).

5.2.1.5 Categories of CNS Involvement at Diagnosis

- CNS 1: CSF has < 5 WBC/μL with cytospin negative for blasts; or > 10 RBC/μL with cytospin negative for blasts.
- CNS 2: CSF has < 5 WBC/μL with cytospin positive for blasts; or > 10 RBC/μL with cytospin positive for blasts;

or ≥ 10 RBC/μL, WBC/μL ≥ 5, but less than Steinharz/Bleyer algorithm with cytospin positive for blasts (see below).

Rev. 2/18

- CNS 3: CSF has ≥ 5WBC/μL with cytospin positive for blasts; or ≥ 10 RBC/μL, ≥ 5 WBC/μL and positive by Steinharz/Bleyeer algorithm (see below); or clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

CNS2 and CNS3 patients who achieve a CR or CRi will receive 1800 cGy cranial radiation in 10 fractions of 180 cGy per fraction during the first cycle of maintenance therapy. See Section 5.6.

Steinharz/Bleyer Method of Evaluating Initial Traumatic Lumbar Punctures:

If the patient has leukemia cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5WBC/μL with blasts, the following algorithm should be used to define CNS disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2\text{X} \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

Example:

A patient with CSF WBC ≥ 5/μL with blasts whose CSF WBC/RBC is greater than twice the blood WBC/RBC ratio has CNS disease at diagnosis. If the CSF WBC=60/μL; CSF RBC=1500/μL; blood WBC=46,000/μL; blood RBC=3 x 106/μL:

$$\frac{60/\mu L}{1500/\mu L} = 0.04, \text{ and is } >2\text{X } \frac{46{,}000/\mu L}{3\text{x}106/\mu L} = 0.015$$

Rev. 6/16

If CNS leukemia (CNS 2 or CNS 3 categories) is present at diagnosis, methotrexate 12.5 mg intrathecally or via an Ommaya Reservoir should be given twice weekly until blasts are not present in the spinal fluid. If the patient subsequently achieves a complete remission, a total dose of 1800 cGy of cranial irradiation in 10 daily fractions of 180 cGy per fraction will be administered during the first cycle of maintenance therapy (Section 5.6).

5.2.1.6 Radiation Therapy and Quality Assurance

Rev. Add14

5.2.1.6.1 Cranial Irradiation for CNS2 and CNS3 Patients

All patients who present with CNS2 and CNS3 leukemia at diagnosis and who achieve a CR will receive cranial radiation

during the first cycle of Maintenance Therapy.

5.2.1.6.2 Equipment and Calibration

- Modality: X-ray beams with a nominal energy between 4 and 6 MV.
- Calibration: Calibration of therapy units used in this protocol will be verified by the Radiological Physics Center (RPC).

5.2.1.6.3 Target Volume

Target volume consists of entire brain and meninges, including frontal lobe as well as posterior halves of globes of eyes, with optic disk and nerve superior to vertex and posterior to occiput. Caudal border will be below skull base at C2 vertebral level.

5.2.1.6.4 Target Dose

- Prescription Point: The prescription point in the cranial volume is at or near the center. For multi-convergent beams, the prescription point is usually at intersection of beam axes.

  NOTE: Regardless of the location of central axis, dose should be prescribed at the center of the cranial volume (midway between the maximum separation).
- Dose Definition: Absorbed dose is specified in centigrays (cGy)-tomuscle.
- Tissue Heterogeneity: No corrections for bone attenuation will be made.
- Prescribed Dose and Fractionation: A total dose of 1800 cGy will be given in 10 daily fractions of 180 cGy per fraction, administered Monday through Friday.

5.2.1.6.5 Dose Uniformity

Dose variations in target volume will be within +7%, -5% of prescription point dose (From ICRU Report 50: small high-dose volumes can be excluded from evaluation of dose uniformity but not small low-dose volumes).

5.2.1.6.6 Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For treatment interruptions greater than 7 days, notify the Study Radiation Oncology Co-Chair.

5.2.1.6.7 Treatment Technique

- Patient Position: It is recommended that the patient be treated in supine position.
- Beam Configuration: Cranial volume is treated with two lateral, equally weighted photon beams. Fields will extend at least 1 cm beyond periphery of scalp.
- Field Shaping: Field-shaping will be done with blocks which are at least 5 HVL thick. Multi-leaf collimators are acceptable.
- Eye Protection: A simple method to minimize lens XRT, while radiating posterior halves of eyes: let central axes of horizontal cranial beams go through both orbits. Anterior edges of beams are defined by external block or by independently controlled collimator and meet at a point 1 cm anterior to frontal lobe meninges. Shielding blocks cover anterior halves of eyes and protect nose and mouth. Essentially the same geometry can be achieved with central axes through center of head by angling lateral fields so rays through the eyes lie in the same horizontal plane. It is acceptable to use parallel-opposed beam pair, without such angling, with shielding blocks that cover anterior half of proximal eye. (Dose to contralateral lens will then increase).

5.2.1.7 Quality Assurance Documentation for Cranial RT

5.2.1.7.1 QARC Post Treatment Review

Patients receiving cranial radiation therapy on this study will have a simple review of the treatment delivered.

There will be no on-treatment review in this study. There is no volume review required.

Within one week of the completion of radiotherapy, the following data shall be submitted:

- RT-2 Radiotherapy Total Dose Record
- A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses

These data should be sent to:

Quality Assurance Review Center
640 George Washington Highway,
Building A, Suite 201
Lincoln, RI 02865
Telephone: (401) 753-7600
Fax: (401) 753-7601
ECOG@QARC.org

Questions regarding the dose calculations or documentation should be directed to:

ECOG-ACRIN Protocol Dosimetrist

Quality Assurance Review Center

Contact information same as above

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5.2.1.7.2 Definitions of Deviation in Protocol Performance

- Prescription Dose Minor Deviation:
  The dose to the prescription point differs from that in the protocol by between 6% and 10%.
- Prescription Dose Major Deviation:
  The dose to the prescription point differs from that in the protocol by more than 10%.

5.2.1.8 All drug doses throughout the protocol are based on the patient's actual weight.

Rev. 3/15

5.2.2 Induction Drug Administration Schedule

Rev. 8/17

NOTE: Please see Section 5.3 for information regarding the substitution of IT cytarabine for IT methotrexate in the case of a methotrexate shortage.

Two Cycles (1 and 2) of induction therapy are used. Doses are based on actual weight.

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5.2.2.1 Cycle 1 Induction - Arm A (28 days)

Cytarabine 70 mg IT Day 1

Daunorubicin 25 mg/m^2 IV push Day 1, 8, 15 and 22

Vincristine 1.4 mg/m^2 IV push Day 1, 8, 15 and 22 (maximum amount 2 mg per dose)

Dexamethasone 10 mg/m^2 PO daily Day 1-7, 15-21 (cap at 20 mg per day; Days 1-7 only if age ≥ 55 years)

Rev. 6/15
Rev. 6/16

Methotrexate 12.5 mg intrathecally day 14 +/- 1 (omit if patient received intrathecal treatment for CNS leukemia as per Section 5.2.1.5).Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

Rev. 8/17

Pegaspargase 2,000 international units/m^2 (IU) IM or IV (recommended) Day 18 (OMIT if age ≥ 55 years) (Cap dose at one vial total, 3750 IU). Premedicate with acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO or IV and hydrocortisone 100 mg IV (hydrocortisone is optional if receiving dexamethasone on the same day).

Rev. 8/17

Rituximab 375mg/m^2 IV infusion Day 8 and 15 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

- HLA Typing and Donor Search

This should be done as soon as possible before or during Cycle 1 of induction chemotherapy if the patient is considered to be a candidate for allogeneic SCT.

- Bone Marrow Aspiration and Biopsy

A bone marrow aspiration and biopsy is performed on Day 28 of induction (or as close to this date as possible) to assess remission status. See Section 5.1 above regarding MRD sample from this marrow. Regardless of the results, Cycle 2 should then be initiated.

FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

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5.2.2.2 Cycle 2 Induction - Arm A (42 Days)

- Cycle 2 of the induction regimen begins on day 29 from start of Cycle 1 induction. It should be postponed until ANC ≥ 0.75 x 10^9/L and platelets > 75 x 10^9/L, whichever is later, in patients with delayed hematologic recovery. If patient has residual disease that is delaying count recovery, cycle 2 can begin immediately.

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- If the ANC and/or platelets fail to recover within 2 weeks of day 28 (i.e., by day 42), contact the study chair or co-chair.
- Therapy should be interrupted for patients who are febrile, neutropenic, and proven infected and resumed at the same point when the signs of infection have abated. Otherwise, therapy during this course should not be interrupted for myelosuppression alone except on day 29. **Hold all of the day 29 chemotherapy of cycle 2 Induction until ANC ≥ 0. 75x10^9 /L and platelets > 75x10^9 /L, then continue chemotherapy to complete the full course of cycle 2 of Induction (no doses of any drugs should be omitted).**

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- Cycle 2 consists of the following:

  Cyclophosphamide 1000 mg/m^2 IV in 250 cc normal saline over 30 min Days 1 and 29. (Patients > 60 years give Cyclophosphamide 800 mg/m^2 per dose)

  Cytarabine 75 mg/m^2/day IV or Sub-Q on Day 1-4, 8-11, 29-32, and 36-39. Intravenous cytarabine can be prepared in 100 cc D5W and given over 30 minutes.

  6-mercaptopurine (6-MP) 60 mg/m2 orally Days 1-14, 29-42 (take at bedtime on an empty stomach 1 hour before or 2 hours after food and/or milk products). Adjust dose using 50 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m2/week. See Appendix IX for details.

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  Pegaspargase 2,000 international units/m^2 (IU) IM or IV (recommended) Day 15 (OMIT if age ≥ 55 years) (cap dose at 1 vial total, 3750 IU). Premedicate with acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO or IV and hydrocortisone 100 mg IV.

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  Methotrexate 12.5 mg intrathecally days 1, 8, 15 and 22 +/- 1 day. These 4 doses should be given even if the patient was treated for CNS 2 or 3 leukemia in cycle 1. Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

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Rituximab 375mg/m^2 IV infusion Day 8 and 15 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

A bone marrow biopsy with cytogenetics should be performed upon blood count recovery to confirm the patient has achieved a CR or CRi. If blood counts are not recovering, a bone marrow biopsy should be done to look for residual disease. If no residual disease noted and counts have not recovered by 4 weeks after day 42 (day 70), contact the study chair or co-chair.

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5.2.2.2.1 Dose Modifications for Initial Induction

- Pegaspargase Related Toxicities

  NOTE: If the patient is allergic to pegaspargase or if pegaspargase is not available, Erwinia-Asparaginase may be substituted.

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Erwinia asparaginase 25,000 international units/m2 (IU/m2) IM or IV 3 times per week for 6 doses for each planned dose of pegaspargase.

Modifications of pegaspargase dosage in the initial Cycle 1 induction treatment should be made as follows:

For each dose of pegaspargase or Erwinia asparaginase, an anaphylaxis kit should be available at the bedside and the patient should be observed for 1 h after IM or IV administration. Steroids, antihistamines, oxygen, and epinephrine should be administered as clinically indicated.

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Read More: http://informahealthcare.com/doi/full/10.3109/10428194.2011.596963

Despite hyperglycemia, the drug should be continued in full doses with insulin administration as indicated. Patients being retreated (8 week gap between

induction, Cycle 1 and intensification) and those receiving infrequent dosing are at increased risk of experiencing anaphylaxis.

Dose modifications of asparaginase for the following toxicities:

a. Pancreatitis – for clinical > grade 2 pancreatitis with elevated serum amylase or lipase and/or radiographic abnormalities, discontinue asparaginase. No further asparaginase should be given.
b. Hyperbilirubinemia – for grade 3 or 4 hyperbilirubinemia withhold asparaginase and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.
c. Deep venous thrombosis or pulmonary embolism – for > grade 3 thrombosis, withhold asparaginase until acute toxicity and clinical signs resolve and consider treatment with fresh frozen plasma or antithrombin III (AT3). Do not withhold dose for abnormal laboratory findings without clinical correlate. Discuss anticoagulant therapy with the study chair if needed. Contact the study chair if considering discontinuation of further asparaginase.
d. Hemorrhage – for > grade 2 hemorrhage in conjunction with hypofibrinogenemia, withhold asparaginase until toxicity is < grade 1. Consider treatment with cryoprecipitate or fresh frozen plasma.
e. Hypertriglyceridemia - For grade 4 hypertriglyceridemia, hold further doses of asparaginase until triglyceride level is < grade 3. Strongly consider therapy with omega-3 fatty acids and a lipid-lowering agent such as gemfibrozil or fenofibrate. Can resume asparaginase if triglyceride level < grade 3.

Contact study chair if additional clarification needed.

Prevention of thrombo-hemorrhagic complications

Practices vary widely in prevention of these complications and range from no screening and prophylaxis to screening and administration of antithrombin III (ATIII) and clotting factors. One suggested approach is to obtain aPTT, PT, ATIII and fibrinogen levels at baseline and to monitor these parameters daily to every few days and to administer cryoprecipitate, 10 units, for fibrinogen levels < 50-100 mg/dL and to administer ATIII for levels < 60-70% of normal. Dosage of AT (THROMBATE III) can be calculated from the following formula (refer to the package insert):

$$\text{units required (IU)} = \frac{[\text{desired} - \text{baseline AT level}] \times \text{weight (kg)}}{1.4}$$

- Hepatic Toxicity

  Daunorubicin and Vincristine doses should be modified on a weekly basis.

Direct Bilirubin	Dose of Vincristine to Give	Dose of Daunorubicin to Give
2 - 3 (mg/dL)	100% calculated	50% calculated
> 3	50% calculated	25% calculated

- Neurotoxicity

  The vincristine dose should be modified to 50% for paresthesia proximal to the DIP joints and stopped entirely for major muscle weakness, cranial nerve palsy or severe ileus.

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- Hematologic Toxicity

  Patients developing anemia may be transfused at the discretion of the investigator. No dose reductions are needed for any degree of anemia or for grade 1-4 neutropenia.

  Similarly, if platelet counts can be maintained by the periodic administration of platelet transfusions, no dose reductions are foreseen for grade 4 thrombocytopenia.

There will be no routine 6-MP dose modifications based on ANC or platelets during induction therapy. It is recommended that patients have their thiopurine methyltransferase (TPMT) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of 6-MP can be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10th to 1/20th the average 6-MP dose. Heterozygotes may need a 30-50% dose reduction of 6-MP. TPMT testing and thiopurine metabolite measurements are commercially available.

Rev. 2/18

NOTE: When administered with allopurinol, the dose of mercaptopurine is reduced to 25%-30% of the usual dose. Allopurinol inhibits xanthine oxidase, which metabolizes mercaptopurine.

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5.2.2.3 Supportive Care

Throughout both cycles of induction therapy, hematopoietic growth factor (HGF) therapy – either G-CSF or GM-CSF - may be used at the investigators discretion. Use of HGF during such therapy should be noted on the data forms.

However, HGF therapy should not be used concurrently with alkylating agents, anthracyclines or antimetabolite chemotherapy drugs.

- Beginning with induction start trimethoprim/sulfamethoxazole prophylaxis. Dose and schedule can be as per local institutional standards. For patients allergic to or experiencing excessive myelosuppression with trimethoprim/sulfamethoxazole, alternative prophylactic regimens including dapsone, atovaquone, or aerolized pentamidine (300 mg monthly via nebulizer).
- Additional antibiotic therapy can be given based on institutional guidelines. Avoid use of voriconazole or posaconazole with vincristine therapy.

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5.2.3 Preservative-Free Methotrexate Shortage Guidelines

The following are guidelines for managing the treatment of enrolled participants on E1910, as well as those individuals who have been

screened, and future participants, when the methotrexate supply is not adequate:

5.2.3.1 For enrolled patients (including those who are consented, but not yet registered/treated)

During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Once an adequate supply of IT methotrexate has been obtained, the patient should be switched back to IT methotrexate in the following cycle.

All other aspects of therapy and monitoring should be followed.

NOTE: This substitution constitutes an unanticipated event that must be reported to the IRB of record. It is very important to document in the research record that the substitution was due to the preservative-free methotrexate shortage.

5.2.3.2 For screened patients (not yet consented) and future patients:

An adequate supply of preservative-free methotrexate, defined as 2 induction cycles worth of methotrexate, must be available for a potential participant prior to consenting and registering the patient to E1910. Institutions whose methotrexate supply is not adequate to cover at least 2 induction cycles worth of therapy for a potential participant must not consent or register new patients into the study until the methotrexate supply issue is resolved.

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5.3 Post-Induction Therapy - Intensification Arm B (28 days)

Patients must have achieved CR or CRi in order to begin intensification therapy. See Section 6 for definitions.

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NOTE: Please see Section 5.3.1.1 for information regarding the substitution of cytarabine, followed the next day by pegaspargase for high dose methotrexate in the case of a methotrexate shortage.

NOTE: If dosing modifications or delays are required during intensification therapy, contact the study chair to discuss.

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Rev. Add14

5.3.1 Intensification Therapy with High Dose Methotrexate

Intensification commences upon achievement of a CR or CRi after the completion of the second cycle of induction (Arm A, Cycle 2). If CR or CRi not achieved and there is no evidence of refractory or relapsed

disease by 4 weeks after end of cycle 2 of induction, contact the study chair or co-chair.

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NOTE: A BONE MARROW ASPIRATE AND BIOPSY WILL BE PERFORMED AT THE TIME OF BLOOD COUNT RECOVERY WHEN PLATELETS > 75 x 10^9/L (> 75,000/mm^3) AND NEUTROPHILS ≥ 0.75x10^9/L (≥ 750/mm^3). IF COUNTS FAIL TO RECOVER WITHIN 6 WEEKS AFTER THE END OF INTENSIFICATION, CONTACT THE STUDY CHAIR. A SAMPLE FOR MRD MUST BE OBTAINED. WITHOUT THIS MRD SAMPLE PATIENTS WILL NOT BE ABLE TO BE RANDOMIZED AND WILL HAVE TO BE TREATED OFF-STUDY.

Methotrexate 3 g/m^2-in 500 ml NS IV over 2 hrs Day 1 and 8

NOTE: With high doses of methotrexate recommend pre-hydration and other supportive care according to the institutional guidelines. In addition, there are potential drug-interactions with methotrexate. Avoid using NSAIDs, trimethoprim/sulfamethoxazole, penicillin, probenecid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin on the same day of MTX.

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NOTE: Order leucovorin as per guidelines below (or may use institutional guidelines for measurement of methotrexate levels and leucovorin dosing). Check methotrexate level at 24 and 48 hours post infusion, and repeat every 24 hours until methotrexate level < 0.1 µmol/L. Order leucovorin as per guidelines below:

Guidelines at 24 hours: If methotrexate level is less than 10 umol/L continue leucovorin at current dosing. If methotrexate level is greater than 10 µmol/L at 24 hours or if creatinine increases greater than 50% of the pre- methotrexate level increase leucovorin to 100 mg/m^2 IV in 100 ml D5W every three hours until methotrexate level is less than 0.1 µmol/L.

Guidelines at 48 hours: If methotrexate level is greater than 1 µmol/L at 48 hours or if creatinine increases greater than 50% of the pre-methotrexate level increase leucovorin to 100 mg/m^2 IV in 100 ml D5W every three hours until methotrexate level is less than 0.1 µmol/L.

Pegaspargase 2,000 IU/m^2 IM (1,000 IU/m^2 age ≥ 55) or IV (recommended) day 9 (Cap dose at one vial total, 3750 IU). Premedicate with acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO or IV and hydrocortisone 100 mg IV. Refer to Section 5.2.2.2.1 for pegaspargase related toxicities and dose modifications.

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Leucovorin Rescue 10 mg/m^2 IV in 50 ml D5W 22-24 hrs after completion of each methotrexate infusion every 6 hrs for 4 doses followed 6 hours later by 10 mg/m^2 orally every 6 hours for 72 hrs.

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NOTE: A BONE MARROW ASPIRATE AND BIOPSY WILL BE PERFORMED AT THE TIME OF BLOOD COUNT RECOVERY. A SAMPLE FOR MRD MUST BE OBTAINED. WITHOUT THIS MRD SAMPLE PATIENTS WILL NOT BE ABLE TO BE RANDOMIZED AND WILL HAVE TO BE TREATED OFF-STUDY. PLEASE ALLOW UP TO 7-10 DAYS IN TREATMENT PLANNING FOR THE PATIENT FOR THE MRD ANALYSIS TO BE COMPLETED AND RESULTS POSTED IN RAVE.

FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

Rev. Add14

NOTE: Only patients who are MRD negative as determined by central assessment in the E-A Leukemia Translational Research Laboratory (LTRL) will be randomized.

Patients who are MRD positive as determined by central assessment in the LTRL will be assigned to Arm C of the protocol and receive blinatumomab.

Patients randomized to receive blinatumomab will proceed to blinatumomab therapy as per Section 5.3.1.1.

Patients randomized to **NOT** receive blinatumomab will proceed directly to consolidation chemotherapy as per Section 5.5.

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5.3.1.1 Preservative-Free Methotrexate Shortage Guidelines

The following are guidelines for managing the treatment of enrolled participants on E1910, as well as those individuals who have been screened, and future participants, when the methotrexate supply is not adequate:

5.3.1.1.1 For enrolled patients (including those who are consented, but not yet registered/treated)

This substitution is for Intensification-Arm B. During a shortage of preservative-free methotrexate, institutions can substitute high dose methotrexate with cytarabine. The dose of **cytarabine** is 2 g/m^2 IV Q12H over 2 hours on day 1 and 8 (or 1 g/m^2 if the patient age > 60). This is followed by **pegaspargase** 1,000 IU/m^2 IM or IV on day 9 (500 IU/m^2 if patient age ≥ 55) (cap dose at one vial total or 3750 IU).

All other aspects of therapy and monitoring should be followed.

NOTE: This substitution constitutes an unanticipated event that must be reported to the IRB of record. It is very important to document in the research record that the substitution was due to the preservative-free methotrexate shortage.

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5.3.1.1.2 For screened patients (not yet consented) and future patients:

An adequate supply of preservative-free methotrexate, defined as 2 induction cycles worth of methotrexate, must be available for a potential participant prior to consenting and registering the patient to E1910. Institutions whose methotrexate supply is not adequate to cover at least 2 induction cycles worth of therapy for a potential participant must not consent or register new patients into the study until the methotrexate supply issue is resolved.

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5.3.2 Blinatumomab Therapy - Arm C: Cycle 1 and 2 (28 days each, with a 14 day break between cycles)

Rev. Add14

NOTE: Patients who are MRD positive as determined by central assessment in the LTRL will be assigned to Arm C of the protocol and receive blinatumomab.

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Blinatumomab therapy commences after recovery from intensification when ANC ≥ 0.75 x 10^9/L and platelets > 75 x 10^9/L.

Patients randomized to blinatumomab will receive two treatment cycles of blinatumomab at a dose of 28 mcg/day by continuous infusion. For dose modifications in case of AEs see Section 5.3.2.2.

NOTE: See Section 5.3.2.2.1 regarding inpatient and outpatient treatment with blinatumomab. It is recommended that patients are hospitalized at least during the first three days

of the first cycle and the first two days of the subsequent cycle.

NOTE: HGF therapy should not be administered during any cycles of blinatumomab therapy.

Rev. Add14

NOTE: A bone marrow aspirate and biopsy will be performed at the time of blood count recovery after the second cycle of blinatumomab. A sample for MRD assessment must be obtained. For MRD assessments, an aspirate from a separate bone marrow aspiration site must be submitted (the needle can be re-directed through the same skin puncture site). Only submit aspirates from the first pull of an aspiration site for MRD testing. Do not submit samples from the second or third pull of the same aspiration site.

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NOTE: MRD positive patients who are assigned to receive blinatumomab should also have a bone marrow biopsy performed at the end of the first cycle of blinatumomab to assess MRD status.

A cycle consists of a continuous IV infusion over four weeks. Cycle 1 of blinatumomab should be followed by a treatment free interval of two weeks before beginning cycle 2 of treatment.

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Blinatumomab should be administered through a central venous access. In the event that administration through a central venous access is not possible, blinatumomab may be administered temporarily through a peripheral venous line if the patient is hospitalized. The final solution for infusion should be administered through a sterile 0.2 µm in-line filter.

The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re-start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be dismissed the following day if no difficulties arise. Administration of the premedication described in Section 5.3.2.1, *Premedication and Concomitant Medication*, is recommended. If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

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NOTE: It should be emphasized to the medical staff and the patient and family regarding the importance of not having any treatment interruption during the blinatumomab therapy to the extent possible

Infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products. All infusion bags may be changed **every 4th day** (not to exceed 96 hours) if preservative-free 0.9% sodium chloride is used in the US and in the

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foreign sites. Shorter time intervals of 24, 48 or 72 hours may also be utilized for convenience of patient scheduling as needed. If bacteriostatic sodium chloride is used, a longer time interval of 7 days (168 hours) for bag changes may be used. See Section 8.1.7 for details.

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5.3.2.1 Pre-Medication and Concomitant Medications

Within one hour prior to start of treatment in each treatment cycle for the prevention of acute reactions to blinatumomab:

- Mandatory administration of dexamethasone (20 mg IV)

During treatment period:

- Patients should receive adequate hydration according to institutional guidelines.

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- Patients will perform a writing test (Appendix VI) which will be evaluated by medical staff and performed at the time of visits for blinatumomab bag changes or weekly clinical visits for evidence of early signs of neurologic toxicity. If changes noted, patients should be monitored and graded for other signs of neurologic toxicity according to CTCAE. The writing test samples can be filed at the center and need not be submitted to ECOG-ACRIN
- Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided if possible because they are a potential cause of endothelial stress.
- Recommended first choice medications for fever management are paracetamol/acetaminophen and/or dexamethasone. The dexamethasone dose should be reduced step-wise as soon as the fever resolves. If these medications are not sufficiently effective, pethidine/meperidine is recommended. For pethidine/meperidine, adequate anti-emetic prophylaxis should be administered.

Fluid Intake/Output Monitoring

Close monitoring of fluid status by intake and output should be undertaken for the first week of blinatumomab infusion. Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) is needed to do this. Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention, some patients will experience pulmonary edema and require more aggressive respiratory support. Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.

Monitoring of Disseminated Intravascular Coagulation (DIC)

In the first days of treatment, transient disseminated intravascular coagulation (DIC)-like pictures may develop. Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone (see Table 5.2 under the "Action" heading), blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care. Particularly in the first week of infusion, when the risk of capillary leak and cytokine release is more prominent, appropriate use of blood products and factors is preferred if laboratory indications suggest the need for replacement, as large volumes of crystalloid fluids tend to exacerbate the capillary leak. See the "Dose Modifications/Infusion Interruptions for Blinatumomab" section for guidelines regarding blinatumomab dose modifications and AE management.

Hematological Monitoring

In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or hemoglobin may be observed. These effects are not necessarily cytokine-mediated. Counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. Transfusion of blood and platelets should be performed according to appropriate institutional standards. Blinatumomab dose modification and AE management guidelines for decreases in neutrophils, lymphocytes, and platelets can be found in the "Dose Modifications/Infusion Interruptions for Blinatumomab" section.

Monitoring of Blood ALT/AST levels

In the first days of treatment, transient increases in transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) up to over 1000 U/L may develop. These have generally returned to baseline in the first week of treatment. Blinatumomab dose modification and AE management guidelines for Grade 3 and 4 increases in ALT or AST can be found in the "Dose Modifications/Infusion Interruptions for Blinatumomab" section.

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5.3.2.2 Dose Modifications/Infusion Interruptions for Blinatumomab

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Before any re-start, for an interruption of 4 hours or longer, the pre-treatment has to be administered as described in Section 5.3.2.1.

Re-start of the infusion should be performed in the hospital, under supervision of the investigator.

Treatment interruptions of up to 28 days for reasons other than adverse events (including but not limited to issues with access to care) are permitted. The reason for the delay must be documented in the patient's record.

Please see table below for determination of treatment cycle duration following treatment interruption for all adverse events.

Table 5.1 Determination of Cycle Length Following Treatment Interruption for Adverse Events

Length of Dose Interruption Due to AE	Length of Treatment Prior to AE Onset	Investigator Action Once Blinatumomab is Restarted
≤ 7 days	-	Continue same cycle of blinatumomab for a total treatment duration of 28 days on blinatumomab
8 to 28 days	≤ 14 days	Cycle of treatment will be re-started as if a new cycle and continue for an additional 28 days total
8 to 28 days	> 14 days	This cycle of treatment will terminated and not be repeated
> 28 days	-	Permanent discontinuation of treatment

NOTE: If the above adverse events resolve to a level allowing resumption of blinatumomab in less than 28 days, but logistical difficulties arise, restart of treatment can be postponed for up to five additional days without resulting in permanent treatment discontinuation.

Table 5.2 Table of Dose Modifications for Adverse Events Possibly, Probably, or Definitely Related to Blinatumomab

Adverse Event (CTCAE v4.0 term)	AE Grade	Action
Events within the "Nervous system disorders" or "Psychiatric disorders" System Organ Class (SOC)*	Grade 1	Continue at same dose level.
	Grade 2	Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days.
	Grade 3	Infusion of the blinatumomab must be stopped immediately. Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Hold blinatumomab until AE resolves to Grade ≤ 1, then resume drug at 9 mcg/day. Subsequent cycles of blinatumomab will be administered at 9mcg/day. Infusion should be re-started in the hospital, under supervision of the investigator and the patient should remain hospitalized for at least two days. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously. At first three days after re-start, vital sign measurements and writing tests should be performed on study days 1- 3. If patient has already been dose reduced to 9 mcg/day dose for any reason and Grade 3 event occurs, blinatumomab should be discontinued permanently.
	Grade 4	Infusion of the blinatumomab must be stopped immediately. Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Blinatumomab should be discontinued permanently.
Seizure	Grade 1-3	As per Grade 3 Nervous System/Psychiatric Disorders (above). Appropriate prophylactic therapeutic doses of anticonvulsant treatment (e.g. phenytoin or levetiracetam) will be administered during subsequent infusions of blinatumomab.
	Grade 4	As per Grade 4 Nervous System/Psychiatric Disorders (above). Appropriate prophylactic therapeutic doses of anticonvulsant treatment (e.g. phenytoin or levetiracetam) will be administered during subsequent infusions of blinatumomab.

Adverse Event (CTCAE v4.0 term)	AE Grade	Action
All other events under "Nervous system disorders" or "Psychiatric disorders" SOC**	Grade 1-4	Continue therapy with supportive care as per institutional guidelines.
Cytokine release syndrome (CRS), Allergic reaction, Anaphylaxis, or Infusion related reaction	Grade 1	Continue therapy with supportive care, as per local institutional guidelines.
	Grade 2	The infusion of the blinatumomab must be stopped immediately. Supportive care, as per institutional guidelines. If the interruption is longer than four hours, re-start of the infusion should be performed in the hospital, under supervision of the investigator. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
	Grade 3	The infusion of the blinatumomab must be stopped immediately. Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Hold blinatumomab until resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously. If Grade 3 recurs after blinatumomab is resumed, stop drug permanently. If the initial adverse event lasts for ≥ 2 weeks without improvement, then blinatumomab will be permanently discontinued.
	Grade 4	Blinatumomab should be discontinued permanently.

Adverse Event (CTCAE v4.0 term)	AE Grade	Action
Aspartate aminotransferase increased, Alanine aminotransferase increased (AST, ALT)	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until AE resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3-4 toxicity recurs, stop drug permanently. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Blood bilirubin increased	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until AE resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3-4 toxicity recurs, stop drug permanently. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Disseminated intravascular coagulation	Grade 2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until AE resolves to Grade ≤ 2, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3-4 toxicity recurs, stop drug permanently. If the initial adverse event lasts for ≥ 2 weeks without improvement, then blinatumomab will be permanently discontinued. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Thromboembolic event	Grade 1	Continue at same dose level.
	Grade 2-4	Hold blinatumomab until clot and clinical situation stabilized, then resume drug at 9 mcg/day for one week. If no progression of thrombus, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If progression of existing thrombosis or new thrombosis or Grade 4 initially, stop drug permanently. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Lymphocyte count decreased	Grade 1-4	Continue at same dose level.

Adverse Event (CTCAE v4.0 term)	AE Grade	Action
Neutrophil count decreased	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until AE resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3 recurs, reduce dose to 9 mcg/day and if after one week toxicity is Grade ≤ 2, continue at 9 mcg/day. If Grade 4 toxicity recurs, stop drug permanently. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Platelet count decreased	Grade 1-3	Continue at same dose level.
	Grade 4	Hold blinatumomab until AE resolves to Grade ≤ 2, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 3, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 4 toxicity recurs, reduce dose to 9 mcg/day and if after one week toxicity is Grade ≤ 2, continue at 9 mcg/day. If Grade 4 toxicity recurs, stop drug permanently. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
All other AEs within the "Investigations" SOC and "Metabolism and nutrition disorders" SOC	Grade 1-4	Continue at same dose level, provided AE is not medically consequential and has been readily corrected. If abnormality is medically consequential, refer to guidelines for other non-hematologic AEs. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption but should receive appropriate medical therapy.
Other non-hematologic AEs	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until AE resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3 recurs, reduce dose to 9 mcg/day and if after one week toxicity is Grade ≤ 2, continue at 9 mcg/day. If Grade 4 toxicity recurs, stop drug permanently. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.

* Please see **Table 5.3** below to assist in determining which adverse events are likely to have a plausible relationship to blinatumomab and require blinatumomab-Specific Dose Modification and Management Guidelines.

** Please see **Table 5.4** below to assist in determining which adverse events are not likely to have a plausible relationship to blinatumomab and require local institutional guidelines.

If a patient experiences one or more of the AEs listed in Table 5.3 below, and the AE(s) is/are determined by the investigator to be possibly, probably, or definitely related to blinatumomab, follow the dose management guidelines for nervous system or psychiatric disorders specified at the top of Table 5.2, above. Note that Seizure (an AE under the "Nervous system disorders" SOC) also has a possible, probable, or definite link to blinatumomab but has a separate set of management guidelines in Table 5.2.

Table 5.3 Adverse Events Under "Nervous system disorders" or "Psychiatric disorders" SOC Requiring Blinatumomab-Specific Dose Modification and Management Guidelines

Nervous system disorders
Aphoria
Amnesia
Cognitive disturbances
Concentration impairment
Depressed level of consciousness
Dysarthria
Dysphasia
Encephalopathy
Memory impairment
Tremor
Psychiatric disorders
Confusion
Delirium
Hallucinations
Psychosis

The events listed in **Table 5.4** below, have been determined by the pharmaceutical collaborator not to have a causal link to blinatumomab. If a patient experiences any of the AEs listed in **Table 5.4** below, they should be treated according to institutional guidelines (i.e., administer antidepressants for depression), and blinatumomab may be held or discontinued as needed for supportive care (such as for Ischemia cerebrovascular).

Table 5.4 Adverse Events Under "Nervous system disorders" or "Psychiatric disorders" SOC Requiring Management According to Normal Institutional Guidelines

Infections and infestations
Cranial nerve infection
Encephalitis infection
Encephalomyelitis infection
Meningitis
Nervous system disorders
Edema cerebral
Headache
Hydrocephalus
Hypersomnia
Ischemia cerebrovascular
Intracranial hemorrhage

Lethargy
Movements involuntary
Neuralgia
Nystagmus
Oculomotor nerve disorder
Paresthesia
Peripheral motor neuropathy
Peripheral sensory neuropathy
Radiculitis
Sinus pain
Somnolence
Transient ischemic attacks
Psychiatric disorders
Agitation
Anxiety
Depression
Euphoria
Insomnia
Mania
Personality change
Psychiatric disorders - Other
Restlessness
any sexual dysfunctions, disturbances, or gender identity disorders

5.3.2.2.1 Inpatient/Outpatient Treatment

Inpatient

Blinatumomab will be administered as a continuous IV infusion over four weeks followed by a two-week treatment free interval. It is recommended that patients are hospitalized at least during the first three days of the first cycle and the first two days of each of the subsequent three cycles. The hospitalization time depends on investigator´s judgment, as well as safety and tolerability of blinatumomab.

The infusion bags will be changed by site nursing personnel. Close monitoring during the first 48 - 72 hours of treatment in the first two cycles will be indicated because of the potential AEs associated with T cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses/physicians trained in critical care medicine should be available for

immediate intervention in case of complications. Afterwards the treatment may be continued on an outpatient basis, if it is judged to be safe and feasible by the investigator.

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Outpatient

In the outpatient setting, several options are available for blinatumomab administration:

1. The patient will return to the study site for all changes of infusion bags.
2. If allowable by the treating physician's institution, infusion bag changes may be performed in the patient's home by an ambulatory/home care service provider. In this case, the ambulatory/home care service provider will be given the remaining bags for the week of treatment that have been prepared by the site investigational pharmacy in a validated shipper for transport. The validated shipper will maintain proper storage conditions during transport for the prepared infusion bags. The infusion bags are to kept/stored at the ambulatory/home care service provider in a controlled temperature monitored refrigerator used at the ambulatory/home care service provider. Patients will be visited by an ambulatory/home care service provider at specific intervals to change the infusion bag. The ambulatory/home care service will be trained and will receive written instruction for transport of drug from the site investigational pharmacy and from the ambulatory/home care service provider to the patient's home for infusion. If necessary shipment of the infusion bags from the site investigational pharmacy to the ambulatory/home care service provider for subsequent transport to the patient's home for infusion will be allowed via use of a validated shipper and a traceable method of shipment via an express courier.
3. If all options above are not feasible, shipping the prepared infusion bags in a

pre-qualified insulated shipper directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable. **Patients are not to open the box upon the receipt of the drug.** Sites interested in utilizing home infusion must contact the E1910 Home Infusion Team at The ECOG-ACRIN Headquarters E1910.homeinfusion@ecogchair.org to initiate set-up for home infusion. See Appendix VIII for additional guidelines of the blinatumomab administration in the outpatient setting.

NOTE: The NCI Drug Accountability Record Form (DARF) must reflect all transaction for preparing and providing the infusion bags to an ambulatory/home care service provider. The ambulatory/home care service provider must also keep DARFs to log in/out date when receiving the infusion bags from the sites and when dispensing the infusion bags to patients as well as the times of all infusion bag changes.

NOTE: The pre-qualified shipper box will include a form of shipment of blinatumomab IV bag(s) to patient's home (See Appendix VIII). That form will be completed by site/pharmacy prior to shipping the IV blinatumomab bags. The home healthcare service will open the box at the time that the IV drug is to be administered to patient. The home healthcare service staff will complete the second portion of the form and any discrepancy must be reported immediately to the site pharmacy. ECOG–ACRIN will submit the completed forms to CTEP.

5.4 Allogeneic SCT

Patients may be taken to allogeneic SCT following completion of blinatumomab therapy or if randomized to the "No Blinatumomab" arm directly following

intensification therapy utilizing any suitable donor and any suitable conditioning regimen (myeloablative, reduced intensity or non-myeloablative) per investigator discretion.

NOTE: It is strongly encouraged that patients randomized to blinatumomab receive both cycles of blinatumomab therapy before proceeding to allogeneic SCT. If only one cycle of blinatumomab is given, then an MRD assessment should be done prior to proceeding to allogeneic SCT.

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NOTE: For Arm C patients, up to 2 cycles of consolidation therapy may be given if there are delays in going to SCT. For Arm D patients, up to 3 cycles of consolidation therapy may be given if there are delays in going to SCT.

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5.5 Consolidation Therapy

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NOTE: Please see Section 5.5.8 for information regarding the substitution of IT cytarabine for IT methotrexate in the case of a methotrexate shortage.

Four-to six courses depending on whether the patient was randomized to blinatumomab (six courses) or no blinatumomab (four courses) of conventional consolidation therapy (after blinatumomab if randomized to it or 4 weeks after intensification if not randomized to blinatumomab) will be administered following intensification therapy for patients who will not receive an allogeneic transplant.

Rev. 3/15

5.5.1 Cycle 1 Consolidation- Arms C & D (28 Days)

Begins after second cycle of blinatumomab (for those randomized to this arm) or after intensification (for those not randomized to blinatumomab) when ANC ≥ 0.75 x 10^9/L and platelets > 75 x 10^9/L, whichever is later.

If the ANC and/or platelets fail to recover within 2 weeks of the end of blinatumomab therapy or within 6 weeks of the end of intensification, contact the study chair or co-chair.

Cytarabine 75 mg/m^2/day IV or Sub-Q on Day 1-5. Intravenous cytarabine can be prepared in 100 cc D5W and given over 30 minutes.

Etoposide 100 mg/m^2 in 500 ml NS IV over 1 hr Day 1-5

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Methotrexate 12.5 mg intrathecally day 1 +/- 1. Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

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Pegaspargase 2,000 IU/m^2 IM (1,000 IU/m^2 if age ≥ 55 years) or IV Day 5

Rev. 2/18

Cap dose at one vial total, 3750 IU

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Rituximab 375mg/m^2 IV infusion Day 5 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

Rev. 8/17
Rev. 2/18

NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

Premedicate with acetaminophen 650 mg PO, diphenhydramine 25 - 50 mg PO or IV and hydrocortisone 100 mg IV. Refer to Section 5.2.2.2.1 for pegaspargase related toxicities and dose modifications.

Rev. 3/15

5.5.2 Cycle 2 Consolidation- Arms C & D (28 Days)

Begins 4 weeks from day 1 of first cycle of consolidation or when ANC ≥ 0.75 x 10^9 /L and platelets > 75 x 10^9/L, whichever is later.

NOTE: If counts fail to recover within 6 weeks from day 1 of the first cycle of consolidation, contact the study chair or co-chair.

Rev. Add14

NOTE: FOR **ARM D** PATIENTS: Bone marrow aspirate and biopsy will be performed after recovery of blood counts from cycle 2 of consolidation for patients on Arm D. A sample for MRD assessment must be obtained. For MRD assessments, an aspirate from a separate bone marrow aspiration site must be submitted (the needle can be re-directed through the same skin puncture site). Only submit aspirates from the first pull of an aspiration site for MRD testing. Do not submit samples from the second or third pull of the same aspiration site.

Cytarabine 75 mg/m^2/day IV or Sub-Q on Day 1-5. Intravenous cytarabine can be prepared in 100 cc D5W and given over 30 minutes.

Etoposide 100 mg/m^2 in 500 ml NS IV over 1 hr Day 1-5

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Rev. 2/18

Methotrexate 12.5 mg intrathecally day 1+/- 1. Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

Rev. 8/17

Rituximab 375mg/m^2 IV infusion Day 5 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

Rev. 8/17
Rev. 2/18

NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

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5.5.3 Cycle 3 Consolidation- Arms C & D (42 Days)

Begins 4 weeks from day 1 of second cycle of consolidation or when ANC ≥ 0.75 x 10^9/L and platelets > 75 x 10^9/L or whichever is later.

NOTE: If counts fail to recover within 6 weeks from day 1 of the second cycle of consolidation, contact the study chair or co-chair.

Daunorubicin 25 mg/m^2 IV push Days 1, 8, 15 and 22

Vincristine 1.4 mg/m^2 IV Days 1, 8, 15, 22 (maximum amount per dose 2 mg)

Cyclophosphamide 650 mg/m^2 in 250 ml NS IV over 30 min, Day 29 only

Cytarabine 75 mg/m^2/day IV or Sub-Q on Days 30-33 and 37-40. Intravenous cytarabine can be prepared in 100 cc D5W and given over 30 minutes.

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6-Mercaptopurine (6-MP) 60 mg/m2 orally Days 29-42 (take at bedtime on an empty stomach 1 hour before or 2 hours after food and/or milk products). Adjust dose using 50 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m2/week. See Appendix IX for details.

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Rev. 2/18

Methotrexate 12.5 mg intrathecally Day 2 +/- 1. Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

Rev. 7/14

Dexamethasone 10 mg/m^2 Days 1-7, 15-21 (cap at 20 mg/day; days 1-7 only if age ≥ 55)

Rev. 8/17

Rituximab 375mg/m^2 IV infusion Day 8 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

Rev. 8/17
Rev. 2/18

NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

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Rev. Add14

5.5.4 Cycle 4 Consolidation - Arm C patients randomized or assigned to blinatumomab (28 days)

Blinatumomab 28 mcg/day, Days 1-28 as per guidelines in Section 5.3.1 and 5.3.1.1. It is recommended that patients be hospitalized for the first two days of this cycle.

Rev. 2/18

Begins 8 weeks following start of consolidation cycle 3 or when ANC ≥ 0.75 x 10^9 /L. and platelets > 75 x 10^9/L, whichever is later.

NOTE: If counts fail to recover within 10 weeks from day 1 of the third cycle of consolidation, contact the study chair or co-chair.

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5.5.5 Cycle 4 Consolidation - Arm D patients randomized to No blinatumomab (28 days)

Begins 8 weeks following start of consolidation cycle 3 or when ANC ≥ 0.75 x 10^9 /L. and platelets > 75 x 10^9/L, or whichever is later.

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NOTE: If counts fail to recover within 10 weeks from day 1 of the third cycle of consolidation, contact the study chair or co-chair.

Cytarabine 75 mg/m^2/day IV or Sub-Q on Day 1-5. Intravenous cytarabine can be prepared in 100 cc D5W and given over 30 minutes.

Etoposide 100 mg/m^2 in 500 ml NS IV over 1 hr Day 1-5

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Rev. 2/18

Methotrexate 12.5 mg intrathecally day 1 +/- 1. Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

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Rituximab 375mg/m^2 IV infusion Day 5 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

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Rev. 2/18

NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

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Rev. Add14

5.5.6 Cycle 5 Consolidation - Arm C patients randomized or assigned to blinatumomab (28 days).

Begins when ANC ≥ 0.75 x 10^9/L and platelets > 75 x 10^9/L, whichever is later.

NOTE: If counts fail to recover within 6 weeks from day 1 of the fourth cycle of consolidation, contact the study chair or co-chair.

Cytarabine 75 mg/m^2/day IV or Sub-Q on Day 1-5. Intravenous cytarabine can be prepared in 100 cc D5W and given over 30 minutes.

Etoposide 100 mg/m^2 in 500 ml NS IV over 1 hr Day 1-5

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Rev. 2/18

Methotrexate 12.5 mg intrathecally day 1 +/- 1. Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

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Rituximab 375mg/m^2 IV infusion Day 5 if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired.

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NOTE: If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

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5.5.7 Cycle 6 Consolidation - Arm C patients randomized or assigned to blinatumomab (28 days).

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Begins 4 weeks following start of consolidation cycle 5 or when ANC ≥ 0.75 x 10^9/L and platelets > 75 x 10^9/L, whichever is later.

NOTE: If counts fail to recover within 6 weeks from day 1 of the fifth cycle of consolidation, contact the study chair or co-chair.

Blinatumomab 28 mcg/day, Days 1-28 as per guidelines in Section 5.3.1 and 5.3.1.1. It is recommended that patients be hospitalized for the first two days of this cycle.

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5.5.8 Preservative-Free Methotrexate Shortage Guidelines

The following are guidelines for managing the treatment of enrolled participants on E1910, as well as those individuals who have been screened, and future participants, when the methotrexate supply is not adequate:

5.5.8.1 For enrolled patients (including those who are consented, but not yet registered/treated)

During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Once an adequate supply of IT methotrexate has been obtained, the patient should be switched back to IT methotrexate in the following cycle.

All other aspects of therapy and monitoring should be followed.

NOTE: This substitution constitutes an unanticipated event that must be reported to the IRB of record. It is very important to document in the research record that the substitution was due to the preservative-free methotrexate shortage.

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5.5.8.2 For screened patients (not yet consented) and future patients:

An adequate supply of preservative-free methotrexate, defined as 2 induction cycles worth of methotrexate, must be available for a potential participant prior to consenting and registering the patient to E1910. Institutions whose methotrexate supply is not adequate to cover at least 2 induction cycles worth of therapy for a potential participant must not consent or register new patients into the study until the methotrexate supply issue is resolved.

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5.6 Maintenance Chemotherapy – Arm E

NOTE: Patients who had evidence of CNS leukemia at diagnosis and subsequently achieved a CR should receive a total dose of 1800 cGy of cranial irradiation in 10 daily fractions of 180 cGy per fraction during the first cycle of maintenance therapy (Section 5.2.1.4).

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NOTE: Please see Section 5.6.11 for information regarding the substitution of IT cytarabine for IT methotrexate in the case of a methotrexate shortage.

Patients completing consolidation will continue on maintenance chemotherapy consisting of:

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6-mercaptopurine (6-MP) 75 mg/m2 orally PO/day continuously (take at bedtime on an empty stomach 1 hour before or 2 hours after food and/or milk products). Adjust dose using 50 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week. See Appendix IX for details.

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Methotrexate 20 mg/m^2 PO or IV once a week

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Vincristine 1.4 mg/m^2 IV day 1 (one dose) every 3 months with prednisone (maximum 2mg/dose)

Prednisone 60 mg/m^2 for days 1-5 PO taken with meals every 3 months

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Methotrexate 12.5 mg intrathecally day 1 +/- 3 days every 3 months.

Hydrocortisone 50 mg intrathecally can optionally combined with methotrexate if desired to lessen the risk of arachnoiditis.

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Maintenance chemotherapy will begin 4-6 weeks after day 1 of the fourth cycle (Arm D) or sixth cycle (Arm C) of consolidation or when ANC ≥ 0.75 x 10^9/L and platelets >75 x 10^9/L, whichever is later. If counts fail to recover within 6 weeks, contact the study chair or co-chair.

NOTE: Maintenance should continue for 2½ years from the start of Intensification therapy (Arm B).

5.6.1 Recommendations for Thiopurine Monitoring and Dosage Adjustments for Myelosuppression

When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing should be performed (If not already done).

- For patients who have received full dose thiopurine during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict the TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status.
- TPMT genotyping will be informative in all patients, if at least one mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5-10% of mutants.

  NOTE: Genotyping can be done despite recent transfusions.

5.6.2 **Dose Adjustments for Patients with Unacceptable Myelosuppression**

- **If the patient is homozygous deficient for TPMT,** the thiopurine dose should be **reduced** to 10-20 mg/m^2/day given 3 days per week.

- **If the patient is heterozygous for TPMT and has experienced significant myelosuppression,** the thiopurine dose should be reduced by 30-50%. Do not increase the dose in response to a high ANC for four weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are often not necessary.

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- **If the patient is homozygous wild-type (high activity) for TPMT and should the ANC fall again below 500/μL on two or more occasions,** follow guidelines in Section 5.6.3 below.

5.6.3 Oral MTX and 6-MP Dose Modifications During Maintenance Therapy for Cytopenias

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- If ANC is < 500/μL, then hold 6-MP and PO MTX until recovery above this level and then resume at full dose once ANC ≥ 750/μL. If ANC is < 500/μL a second time, discontinue 6-MP and PO MTX until ANC ≥ 750/μL. Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose in 2-4 week intervals provided ANC ≥ 750/μL. Consider discontinuing cotrimoxazole and switching patient to dapsone or pentamidine. If ANC < 500/μL on ≥ 2 occasions during Arm E, perform thiopurine pharmacology testing (see Section 8.4.2). Investigators may proceed at their own discretion or contact the study chair or co-chair to discuss how to proceed. Should therapy be withheld for myelosuppression, do not "make up" that week. Resume therapy at the correct point chronologically.

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- If platelet count is < 75,000/μL, then hold 6-MP and PO MTX until recovery above this level and then resume at full dose once platelets ≥ 75,000/μL. If platelet count is < 75,000/μL a second time, discontinue 6-MP and PO MTX until platelets ≥ 75,000 μL. Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided platelets ≥ 75,000/μL. Consider discontinuing cotrimoxazole and switching patient to dapsone or pentamidine. If platelets < 75,000/μL on ≥ 2 occasions during Arm E, perform thiopurine pharmacology testing (see Section 8.4.2). Investigators may proceed at their own discretion or contact the study chair or co-chair to discuss how to proceed. Should therapy be withheld for myelosuppression, do not "make up" that week. Resume therapy at the correct point chronologically.
- Patients experiencing myelosuppression should have their TPMT status and/or their thiopurine metabolite concentrations evaluated, so that the dose of 6-MP can be reduced in patients with TPMT defect.

5.6.4 Oral MTX and 6-MP Dose Escalation During Maintenance Therapy

For ANC ≥ 1500/μL, on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s), first increase the dose of either PO MTX or 6-MP by 25%. Then increase the dose of the other drug by 25%. If there is no fall in ANC after both PO MTX and 6-MP have been increased once, consider noncompliance is a possibility. Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4 hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance. **If oral MTX dose is escalated to 40 mg/m^2, contact the Study Chair before further escalation.**

5.6.5 Oral or IV MTX Dose Reductions During Maintenance Therapy for Elevated Bilirubin

If direct bilirubin > 2.0 mg/dL, then hold IV or oral MTX. When direct bilirubin ≤ 2 mg/dL, then resume MTX at the previous dose.

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5.6.6 Oral MTX Dose Modifications for Maintenance Therapy for Elevated Transaminases

- For increase in ALT or AST > 5 x ULN, obtain direct bilirubin. Monitor ALT or AST and direct bilirubin every 4 weeks during Maintenance Therapy (Arm E) as long as transaminases remain > 5 x ULN.
- If ALT or AST > 20 x ULN on two determinations at least one week apart or direct bilirubin > 2 mg/dL, hold MTX and monitor labs weekly. When ALT or AST is < 5 x ULN and direct bilirubin is within normal, then resume at the previous dose.

Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in ALT or AST.

5.6.7 Oral MTX Dose Modifications for Mucositis During Maintenance Therapy

- For grade 3 mucositis, PO MTX should be given at 50% of the previous dose.
- For grade 4 toxicity, PO MTX should be temporarily held. Once toxicity resolves, then resume PO MTX at 50% of the previous dose. PO MTX should then be escalated as tolerated. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

5.6.8 Oral MTX Dose Modifications for Diarrhea and Vomiting During Maintenance Therapy

If either severe diarrhea or vomiting develops after PO MTX administration, PO MTX should be temporarily held. After resolution of symptoms (i.e., < grade 2) for a period of one week, resume PO MTX at 50% of the previous dose. PO MTX should then be escalated as tolerated. If symptoms recur, adjust the dose to the maximum tolerated to prevent recurrent symptoms. The patient should be evaluated for infectious as well as other causes of diarrhea and vomiting.

5.6.9 Dose Modifications for Renal/Genitourinary Toxicity During Maintenance Therapy

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- For ≥ grade 2 creatinine level increase, hold PO MTX until toxicity resolves to ≤ grade 1. Once toxicity has resolved to this level, then PO MTX may be resumed at the previous dose.
- For ≥ grade 2 creatinine level increase, hold 6-MP until toxicity resolves to ≤ grade 1. Once toxicity has resolved to this level, then 6-MP may be resumed at the previous dose.

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5.6.10 Dose Modifications for Other Toxicity During Maintenance Therapy (at investigator discretion)

For ≥ grade 2 symptoms believed due to PO MTX or requiring cessation of PO MTX despite optimal supportive care, hold PO MTX until toxicity resolves to ≤ grade 1. Once toxicity has resolved to this level, then PO MTX may be resumed at the starting dose.

For ≥ grade 2 symptoms believed due to 6-MP or requiring cessation of 6-MP despite optimal supportive care, hold 6-MP until toxicity resolves to ≤ grade 1. Once toxicity has resolved to this level, then 6-MP may be resumed at the starting dose.

If the same toxicity recurs at ≥ grade 2 with resumption of previous dose, then hold PO MTX and/or 6-MP until toxicity resolves to <grade 1 then restart PO MTX and/or 6-MP at a 25% dose reduction from the previous dose.

If the same toxicity does not recur at grade 2 or higher within 28 days of resumption of PO MTX and/or 6-MP, then dose may be increased to the previous dose level at the investigator's discretion. This may be repeated every 28 days up to the starting dose.

If omission or dose reduction of a drug is desired, contact study chair for guidance.

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5.6.11 Preservative-Free Methotrexate Shortage Guidelines

The following are guidelines for managing the treatment of enrolled participants on E1910, as well as those individuals who have been screened, and future participants, when the methotrexate supply is not adequate:

5.6.11.1 For Enrolled patients (including those who are consented, but not yet registered/treated)

During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Once an adequate supply of IT methotrexate has been obtained, the patient should be switched back to IT methotrexate in the following cycle.

All other aspects of therapy and monitoring should be followed.

NOTE: This substitution constitutes an unanticipated event that must be reported to the IRB of record. It is very important to document in the research record that the substitution was due to the preservative-free methotrexate shortage.

5.6.11.2 For screened patients (not yet consented) and future patients:

An adequate supply of preservative-free methotrexate, defined as 2 induction cycles worth of methotrexate, must be available for a potential participant prior to consenting and registering the patient to E1910. Institutions whose methotrexate supply is not adequate to cover at least 2 induction cycles worth of therapy for a potential participant must not consent or register new patients into the study until the methotrexate supply issue is resolved.

5.7 Supportive Care Considerations

Supportive care regarding adequate hydration and use of antiemetics for nausea and vomiting should be supplied according to institutional guidelines.

5.7.1 Hematopoietic Growth Factor (HGF) Therapy

Throughout both cycles of induction chemotherapy, consolidation chemotherapy and maintenance chemotherapy, HGF therapy - either G-CSF or GM-CSF - may be used at the investigators discretion. Use of CSF during such therapy should be noted on the data forms.

NOTE: However, HGF therapy should not be used concurrently with alkylating agents, anthracyclines or antimetabolite chemotherapy drugs.

HGF therapy should also not be administered during any cycles of blinatumomab therapy.

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5.8 Adverse Event Reporting Requirements

NOTE: Effective April 1, 2018, expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines in this protocol will continue to be based on CTCAE version 4.0 terminology and grading.

NOTE: CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be

downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

5.8.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.8.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.8.3 Reporting Procedure

This study requires that expedited adverse event reporting use the CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900) for all treatment Arms
- the NCI (301-897-7497) for all treatment Arms
- the FDA (1-800-FDA-1088) for Arms A, B, D and E (only if previously NOT on Blinatumomab)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

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Supporting and follow up data: Any supporting or follow-up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301-897-7404) for all

treatment Arms and FDA (800-332-0178) for Arms A, B, D and E (only if previously NOT on Blinatumomab) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.8.4 Determination of Reporting Requirements

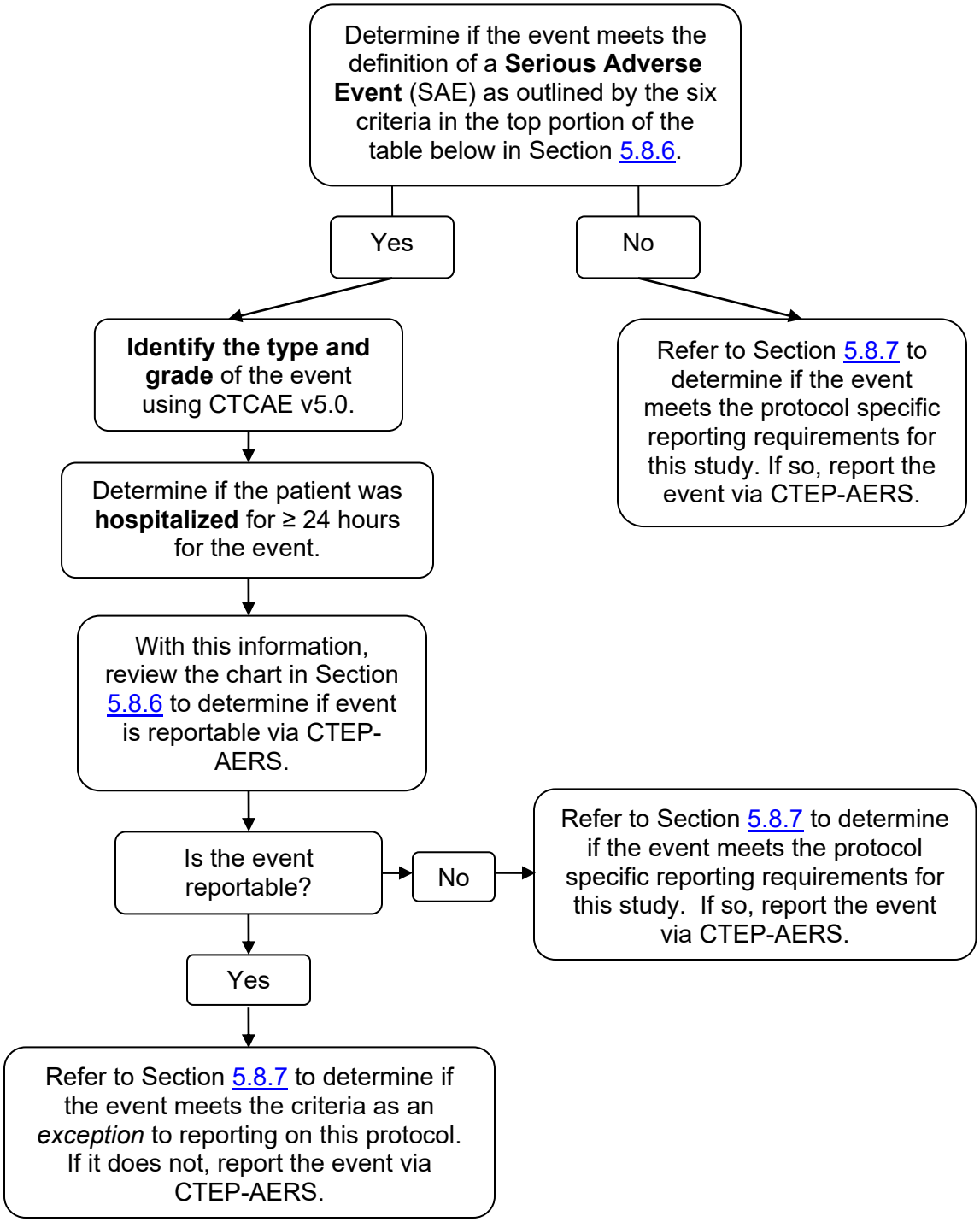
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E1910 and outline the specific expedited adverse event reporting requirements for study E1910.

5.8.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arm C and E (for those previously on Blinatumomab)

5.8.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.8.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.8.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.8.6 Expedited Reporting Requirements for Arm C and E (for those previously on Blinatumomab) on protocol E1910

Investigational Agents: Blinatumomab

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Commercial Agents: Vincristine, Prednisone, 6 Mercaptopurine, Methotrexate, PEG-Asparaginase, Cytarabine, Etoposide, Daunorubicin, Dexamethasone, Cyclophosphamide, Rituximab

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

5.8.7 Additional instructions, requirements and exceptions for protocol E1910

Additional Instructions:

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

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- **Reporting a death on study:** A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causalty. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

E1910 specific expedited reporting requirements:

- **Pregnancy**

  Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Blinatumomab, or within 28 days of the subject's last dose of Blinatumomab, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

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- **Infection**

  Any grade 3 or higher infection (defined as sepsis, bacteremia, device or catheter-related infection) that occurs while the patient is on protocol treatment or within 30 days of the last administration of the investigational agent, regardless of attribution, must be reported via CTEP-AERS according to the timeframes outline in the AE table in Section 5.8.6. Any grade 3 or higher infection (defined as sepsis, bacteremia, device or catheter-related infection) that occurs more than 30 days after the last administration of the investigational agent and has an attribution of possible, probable, or definite must also be reported via CTEP-AERS.

E1910 specific expedited reporting exceptions:

For study arms C and E (for those previously on Blinatumomab), the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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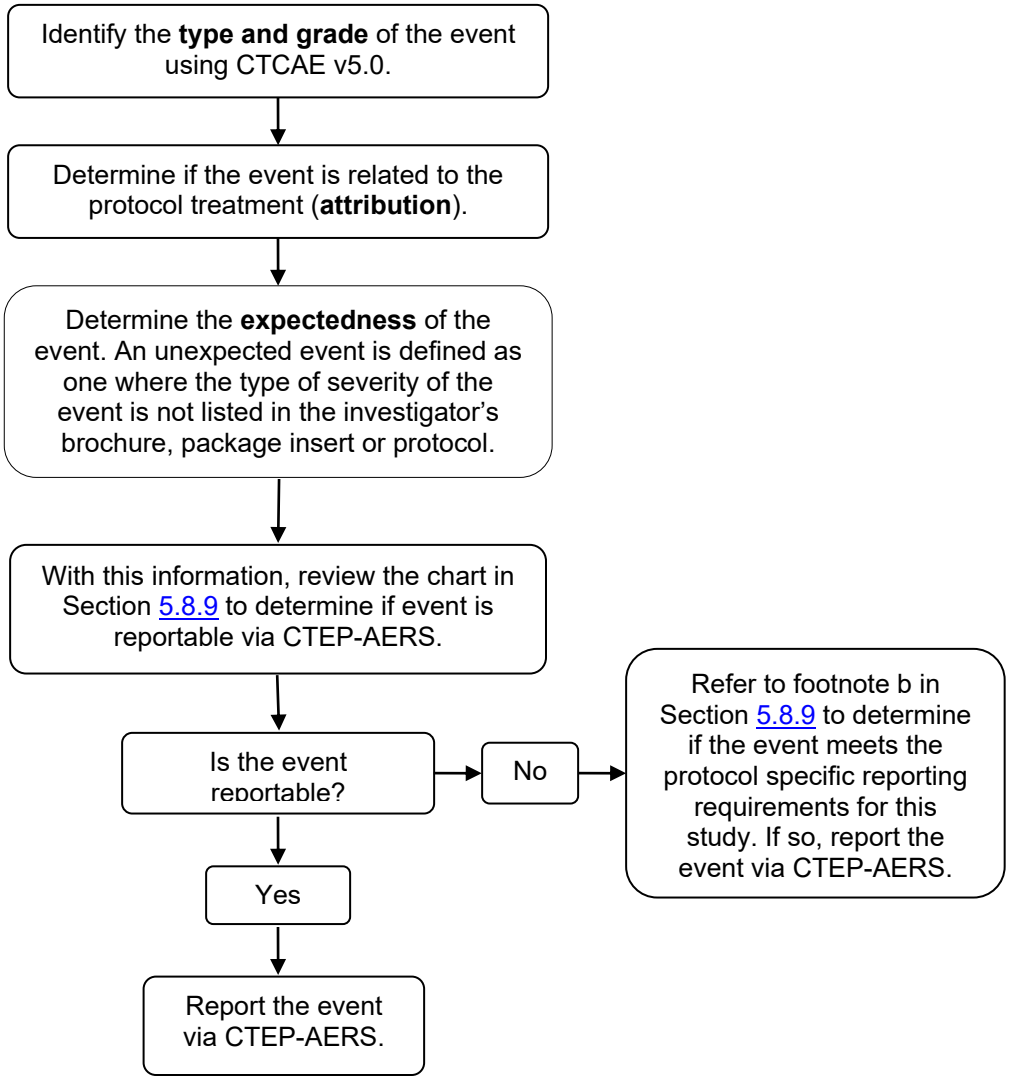
- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.8.8 Steps to determine if an event is to be reported in an expedited manner - Arms A, B, D and E (for those previously NOT on Blinatumomab)



5.8.9 Expedited Reporting Requirements for Arms A, B, D and E (for those NOT previously on Blinatumomab) on protocol E1910

Commercial Agents: Vincristine, Prednisone, 6 Mercaptopurine, and Methotrexate, PEG-Asparaginase, Cytarabine, Etoposide, Daunorubicin, Dexamethasone, Cyclophosphamide, Leucovorin, Rituximab

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Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only					
Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	
7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.					

Rev. Add14

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided. **NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted. NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event**.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

5.8.10 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.8.11 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     - Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.9 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Blinatumomab (AMG103, NSC 765986)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 1276 patients. Below is the CAEPR for Blinatumomab (AMG 103).

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NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER

NOTE: Although grade 4 infections are listed as an exception to expedited reporting in the SPEER column below, all grade 3 and high infections (defined as sepsis, bacteremia, device or catheter-related infection) must still be reported per section 5.8.7

Version 2.5, September 4, 2019[1]

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
	Blood and lymphatic system disorders - Other (coagulopathy)[2]		***Blood and lymphatic system disorders - Other (coagulopathy)[2] (Gr 2)***
		Blood and lymphatic system disorders - Other (hematophagic histiocytosis)	
		Blood and lymphatic system disorders - Other (lymphadenitis)	
		Blood and lymphatic system disorders - Other (lymphadenopathy)	
		Blood and lymphatic system disorders - Other (pancytopenia)	
	Disseminated intravascular coagulation[2,3]		***Disseminated intravascular coagulation[2,3] (Gr 2)***

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
	Sinus tachycardia		***Sinus tachycardia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
		Gastric hemorrhage	
		Gastrointestinal disorders - Other (pneumoperitoneum)	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
		Oral hemorrhage	
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[3]		***Chills[3] (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue[3]			***Fatigue[3] (Gr 2)***
Fever[3]			***Fever[3] (Gr 2)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatic function abnormal)[4]		***Hepatobiliary disorders - Other (hepatic function abnormal)[4] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
	Cytokine release syndrome[3]		***Cytokine release syndrome[3] (Gr 3)***
	Immune system disorders - Other (immunodeficiency [immunoglobulin decreased])[5]		***Immune system disorders - Other (immunodeficiency [immunoglobulin decreased])[5] (Gr 2)***
INFECTIONS AND INFESTATIONS			
Infection[6]			***Infection[6] (Gr 4)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
		Injury, poisoning and procedural complications - Other (overdose)[7]	

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS			
		Activated partial thromboplastin time prolonged[2]	
	Alanine aminotransferase increased[4]		***Alanine aminotransferase increased[4] (Gr 3)***
	Alkaline phosphatase increased[4]		***Alkaline phosphatase increased[4] (Gr 2)***
	Aspartate aminotransferase increased[4]		***Aspartate aminotransferase increased[4] (Gr 4)***
	Blood bilirubin increased[4]		***Blood bilirubin increased[4] (Gr 2)***
	Blood lactate dehydrogenase increased		
		Creatinine increased[8]	
	GGT increased[4]		***GGT increased[4] (Gr 2)***
		Investigations - Other (blood fibrinogen increased)[2]	
	Investigations - Other (C-reactive protein increased)		***Investigations - Other (C-reactive protein increased) (Gr 2)***
	Investigations - Other (fibrin D dimer increased)[2]		
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased[2]			***Platelet count decreased[2] (Gr 2)***
	Weight gain		***Weight gain (Gr 2)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hyperuricemia		
	Hypoalbuminemia		
	Hypocalcemia		

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Hypokalemia			***Hypokalemia (Gr 2)***
	Hypomagnesemia		
	Hypophosphatemia		
		Tumor lysis syndrome[9]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Bone pain		
	Generalized muscle weakness		
	Myalgia		
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Ataxia[10]		
	Cognitive disturbance[10]		
	Dizziness[10]		***Dizziness[10] (Gr 2)***
		Dysarthria[10]	
	Dysphasia[10]		
	Encephalopathy[10]		
		Facial nerve disorder[10]	
Headache[10]			***Headache[10] (Gr 2)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
	Memory impairment[10]		
	Nervous system disorders - Other (apraxia)		
	Nervous system disorders - Other (cerebellar syndrome)[10]		
		Nervous system disorders - Other[10]	
	Paresthesia[10]		
		Reversible posterior leukoencephalopathy syndrome	
	Seizure[10]		
	Somnolence[10]		
		Transient ischemic attacks[10]	
	Tremor[10]		***Tremor[10] (Gr 2)***
PSYCHIATRIC DISORDERS			
		Agitation[10]	
	Anxiety[10]		

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Confusion[10]		
		Hallucinations[10]	
	Insomnia		***Insomnia (Gr 2)***
		Personality change[10]	
		Psychosis[10]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Epistaxis		
		Hypoxia	
	Oropharyngeal pain		
		Pneumonitis	
	Voice alteration[10]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		
	Pruritus		
	Skin and subcutaneous tissue disorders - Other (rash)[11]		***Skin and subcutaneous tissue disorders - Other (rash)[11] (Gr 2)***
VASCULAR DISORDERS			
		Capillary leak syndrome[3]	
	Flushing[3]		
	Hypertension[3]		***Hypertension[3] (Gr 2)***
	Hypotension[3]		***Hypotension[3] (Gr 2)***
	Thromboembolic event[2]		***Thromboembolic event[2] (Gr 2)***

Rev. Add15 [1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV . Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Blinatumomab (AMG 103) is known to cause a variety of adverse events associated with coagulopathy which may include: Activated partial thromboplastin time prolonged, Disseminated intravascular coagulation, Fibrinogen decreased, INR increased, Investigations - Other (blood fibrinogen increased), Investigations - Other (fibrin D dimer increased), Investigations - Other (activated partial thromboplastin time shortened), Investigations - Other (antithrombin III decreased), Investigations - Other (coagulation factor XII level decreased), Investigations - Other (coagulation factor XIII level increased), Investigations - Other (haptoglobin decreased), Investigations - Other (protein S decreased), Platelet count decreased, and Thromboembolic events.

[3] Symptoms of cytokine release syndrome (CRS) and/or allergic reaction may include chills, fever, fatigue, flushing, bronchospasm, and hypotension. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

[4] Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTIGATIONS SOC.

[5] Immunodeficiency (immunoglobulin decreased) includes immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and blood immunoglobulin A decreased.

[6] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[7] Overdoses have been observed. Overdoses resulted in adverse reactions, which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care. Consider re-initiation of blinatumomab at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion

[8] Acute kidney injury (acute renal failure) is associated with increased creatinine levels.

[9] Tumor lysis syndrome is defined as a massive overload of potassium, phosphate, uric acid, plus hypocalcemia, potentially causing lethal cardiac arrhythmias and/or renal failure.

[10] Blinatumomab (AMG103) is known to cause a variety of nervous system disorders which may include: Ataxia, Cognitive disturbance, Concentration impairment, Depressed level of consciousness, Dizziness, Dysphagia, Dysarthria, Dysesthesia, Dysphasia, Encephalopathy, Facial nerve disorder, Headache, Lethargy, Memory impairment, Paresthesia, Peripheral sensory neuropathy, Seizure, Somnolence, Syncope, Transient ischemic attacks, Tremor, Voice alteration, Nervous system disorders - Other (allodynia), Nervous Systems disorders - Other (cerebellar syndrome), Nervous system disorders - Other (dysgraphia), Nervous system disorders - Other (epilepsy), Nervous system disorders - Other (facial palsy), Nervous system disorders - Other (hemiparesis), Nervous system disorders - Other (hypertonia), Nervous system disorders - Other (hypotonia), Nervous system disorders - Other (pleocytosis), and Nervous system disorders - Other (polyneuropathy). Additionally, symptoms of some nervous system disorders are adverse events under the PSYCHIATRIC DISORDERS SOC and may include: Agitation, Anxiety, Confusion, Hallucinations, Personality change, and Psychosis.

[11] Rash includes rash, rash maculo-papular, erythema, local erythema, erythematous rash, generalized rash, exanthema, allergic dermatitis, and palmar-plantar erythrodysesthesia syndrome.

Adverse events reported on blinatumomab (AMG 103) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that blinatumomab (AMG 103) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Sinus bradycardia; Supraventricular tachycardia

CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (aplasia)

EAR AND LABYRINTH DISORDERS - Vertigo

EYE DISORDERS - Blurred vision; Optic nerve disorder; Papilledema; Periorbital edema; Photophobia

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Dyspepsia; Dysphagia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (thrombosis in device); Hypothermia; Malaise; Multi-organ failure

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Vascular access complication

INVESTIGATIONS - Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hypoproteinemia); Investigations - Other (lipase decreased); Lipase increased; Lymphocyte count increased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperkalemia; Hyperphosphatemia; Hyponatremia; Metabolism and nutrition disorders - Other (fluid overload)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Muscle cramp; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Amnesia; Facial muscle weakness; Muscle weakness left-sided; Nervous system disorders - Other (difficulty following commands); Neuralgia

PSYCHIATRIC DISORDERS - Delirium; Depression; Psychiatric disorders - Other (altered mental status); Psychiatric disorders - Other (sleep disorder); Restlessness

RENAL AND URINARY DISORDERS - Acute kidney injury[7]; Hematuria; Proteinuria; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm[3]; Pleural effusion; Productive cough; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Purpura; Skin and subcutaneous tissue disorders - Other (skin irritation)

VASCULAR DISORDERS - Hematoma

NOTE: Blinatumomab (AMG 103) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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5.10 Duration of Therapy

Patients will receive protocol therapy unless:

5.10.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E1910 Forms Packet.

5.10.2 Patient withdraws consent.

5.10.3 Patient experiences unacceptable toxicity.

5.10.4 Non-protocol therapies are administered.

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5.10.5 Failure to achieve CR or CRi (Sections 6.1 and 6.2) after completion of Cycles 1 and 2 Induction-Arm A.

5.10.6 Relapse of leukemia at any time after achieving a CR or CRi.

5.11 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for 10 years from the start of treatment, even if non-protocol therapy is initiated, and for survival.

6. Measurement of Effect

6.1 Complete Remission (CR)

Requires that all of the following be present

6.1.1 Peripheral Blood Counts

6.1.1.1 Neutrophil count ≥ 1.0 x 10^9/L (≥ 1000/mm^3)

6.1.1.2 Platelet count ≥ 100 x 10^9/L (≥ 100,000/mm^3)

6.1.1.3 Reduced hemoglobin concentration or hematocrit has no bearing on remission status.

6.1.1.4 Leukemic blasts must not be present in the peripheral blood.

6.1.2 Bone Marrow Aspirate and Biopsy

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6.1.2.1 Adequate bone marrow cellularity with trilineage hematopoiesis.

6.1.2.2 ≤ 5% blasts.

6.1.3 Extramedullary leukemia, such as CNS or soft tissue involvement, must not be present.

6.2 Complete Remission incomplete (CRi)

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All the same response criteria in peripheral blood and bone marrow as CR with the exception that there is incomplete platelet recovery (platelets > 75 but <100 x 10^9/L (> 75,000 but < 100,000/mm^3) independent of platelet transfusions) or incomplete neutrophil count recovery > .75 but < 1 x 10^9/L (> 750 but < 1000/mm^3).

6.3 Partial Remission (PR)

6.3.1 Requires that all of the criteria for complete remission be satisfied except that the bone marrow may contain > 5% blasts but < 25% blasts.

6.4 Relapse/Persistent Disease

Rev. 3/15, 8/17

Persistent disease/Relapse following complete remission (CR)/complete remission incomplete (CRi) is defined as:

6.4.1 Peripheral Blood Counts

6.4.1.1 Reappearance or persistence of blasts in the blood.

6.4.2 Bone Marrow Aspirate and Biopsy

6.4.2.1 Presence of > 5% blasts, not attributable to another cause (e.g., bone marrow regeneration).

Rev. 8/17

6.4.3 In the case of isolated CNS relapse such as a positive cytospin examination of CSF, please consult with Study Chair. Perform bone marrow biopsy (if not already done) to confirm presence or lack of medullary relapse.

7. Study Parameters

7.1 Therapeutic Parameters

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All prestudy scans and x-rays should be done ≤ 4 weeks before registration.

1. Prestudy scans or x-rays used to document measurable or evaluable disease should be done within 2 weeks of registration.
2. Prestudy CBC with differential, LFTs should be done ≤ 48 hours before registration.
3. All required prestudy chemistries should be done ≤ 1 week before registration - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours prior to registration. Serum creatinine and total/direct bilirubin must be completed ≤ 48 hours before registration.
4. Pre-study bone marrow biopsy and aspirate and/or blood samples must be completed ≤ 1 week prior to registration.

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Rev. Add14

Table 1. Study Parameters

Rev. 7/14

	Cycle 1 Induction			Prior to Cycle 2	Intensification			Post Intensification	During Cycles 1 and 2 Blinatumomab	Post Blinatumomab
	Prior	Daily	Weekly		Prior	Daily	Weekly		Weekly	
History and Physical	X	X[1]		X	X				X	
Rev. Add15 Weight and Height	X			X	X				X	
CBC with Differential [2]	X	X[1]		X	X	X[1]		X	X	X
HLA typing[3]	X									
Serum Sodium, Potassium, Calcium, Serum Creatinine, Phosphate, Magnesium, Urates	X	X[5]	X	X	X		X		X	
Rev. 6/15 Serum Direct or Total Bilirubin, SGPT (AST), SGPT (ALT), Alkaline Phosphatase, LDH	X	X[9]	X[9]	X	X		X		X	
Rev. 3/15 PT, aPTT, Fibrinogen, D-dimer	X		X[6]	X			X[6]			
Antithrombin III			X[6]				X[6]			
Triglycerides			X[6]				X[6]			
Amylase, Lipase			X[6]				X[6]			
Chest X-ray	X									
Lumbar puncture	X[10]			X[10]						
ECG	X									
Cardiac Ejection Fraction (MUGA/Echocardiogram)[4]	X									
Bone Marrow Aspirate, Biopsy and Cytogenetics	X			X	X[18]			X[19]		X[21]
Rev. 3/15 *Serum or Urine* Pregnancy Test [7]	X									
Writing Test [12]									X	
Rev. 8/17 HBsAG, anti-HBc	X									
Biological Sample Submissions	See Sections 7.2 and 10									

	Allogeneic SCT			Post – Allogeneic SCT	With each Consolidation Cycle			During Cycles 4 and 6 Blinatumomab	Prior to and during Maintenance	Follow-Up[16]
	Prior	Daily	Weekly		Prior	Daily	Weekly	Weekly		
History and Physical	X				X			X		
Weight and Height (height baseline only)	X				X			X		
CBC with Differential [2]	X	X[1]		X[16]	X	X[1]		X	X[13]	X
HLA typing[3]										
Serum Sodium, Potassium, Calcium, Creatinine, Phosphate, Magnesium, Urates	X	X[8]			X		X	X	X[14]	
Serum Direct or Total Bilirubin, SGPT (AST), SGPT (ALT), Alkaline Phosphatase, LDH	X	X[8]			X		X	X	X[14]	
PT, aPTT, Fibrinogen, D-dimer							X[6]			
Antithrombin III							X[6]			
Triglycerides							X[6]			
Amylase, Lipase							X[6]			
Chest X-ray										
Lumbar puncture										
ECG										
Cardiac Ejection Fraction (MUGA/Echocardiogram)[4]										
Rev. Add14 Bone Marrow Aspirate, Biopsy and Cytogenetics	X			X[17]	X[20]				X[15]	X[17]
Serum or Urine Pregnancy Test [7]										
Writing Test [12]								X		
Rev. 8/17 HBsAg. anti-HBc										
Biological Sample Submissions	See Sections 7.2 and 10									

1. The daily evaluations should be performed until discharge from the hospital. If the patient is discharged prior to recovery of ANC or platelet count the values should be obtained no less than twice weekly until the outcome BM is performed
2. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.
3. For patients who are considered to be SCT candidates. High resolution class I and class II typing should be performed.
4. If a cardiac ejection fraction cannot be obtained due to weekend or holiday then patients may be enrolled provided there are no clinical signs or there is no history of significant cardiovascular disease and a measurement of cardiac ejection fraction will be performed within 5 days of study enrollment.
5. Monitoring for tumor lysis syndrome at the initiation of induction therapy is strongly suggested at least every 8-12 hours for at least the first 3-5 days of treatment, and at further intervals at the discretion of the investigator.

6. Suggested but not required to monitor for coagulopathy related to pegaspargase use.
7. For women of childbearing potential.
8. Twice weekly and as indicated.

Rev. 8/17
9. At least 2x a week during induction chemotherapy, more often as needed.

Rev. 3/15, 8/17
10. As per schedule outlined in Section 5. Initial lumbar puncture is done on Day 1 of Induction Arm A (see Section 5.2.2) and does **not** need to be done prior to registration. If the patient received IT chemotherapy within 5 days of enrollment and received lumbar puncture with cytology and cell count, the lumbar puncture does not need to be performed on Day 1 of Induction.

Rev. 3/15
12. To be done and checked by medical staff seeing patient at each time of assessment See Appendix VI for writing test form.
13. Monthly and as clinically indicated.
14. Every 3 months and as clinically indicated.

Rev. 6/15, 8/17
15. Prior to maintenance and every 6 months for 2 years or until the end of maintenance Karyotype analysis is optional.

Rev. 7/14
16. Patients will be followed at the following time points: every 3 months (90 days) if patient is < 2 years from study entry, every 6 months (180 days) if patient is 2-5 years from study entry, every 12 months (365 days) if patient is 6-10 years from study entry. Patients will be followed for both survival and relapse.
17. 2-3 months after the end of all therapy, at relapse, and as clinically indicated.

Rev. 3/15
18. Blood count recovery to confirm CR or CRi. If blood counts are not recovering, bone marrow should be done to look for residual disease.

Rev. 3/15
19. Perform marrow upon blood count recovery when platelets >75x10^9/L (> 75,000/mm^3) and neutrophils >0.75x10^9/L (>750/mm^3). If counts fail to recover within 6 weeks after the end of intensification, contact the study chair.

Rev. Add14
20. Bone Marrow Aspirate, Biopsy, Cytogenetics to be done post cycle 2, prior to cycle 3 for patients on Arm D.
21. Bone Marrow Aspirate and Biopsy should be done for MRD positive patients assigned to Arm C after both cycles 1 and 2 of blinatumomab.

Rev. 7/14
Rev. 6/16

7.2 Biological Sample Submissions

Rev. 3/15

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

	Pre-Registration[2]	Prior to Start of Treatment (Step 1)	Post Cycle 1 of Induction Chemotherapy (day 28)	Post Cycle 2 of Induction Chemotherapy (at time of count revcovery)	Prior to Randomization / Post Intensification	Post Cycle 1 of Blinatumomab	Post Initial 2 Cycles of Blinatumomab (Prior to Cycle 3 / Post Cycle 2 of Consolidation for those on Arm D)	Prior to Cycle 4 of Consolidation with Blinatumomab (Cycle 3 of Blinatumomab)	Post Consolidation / Prior to Start of Maintenance	Relapse[15]	Submit to:
	MANDATORY for Central Diagnostic Review and Defined Laboratory Research Studies										
Rev. Add14 Bone Marrow Aspirate for MRD (heparin, FIRST PULL)[3]	X		X	X[16]	X[11]	X[5] (MRD Positive Pts at Step 3 Registration & HSCT patients only)	X[12]			X	LTRL[1]
Peripheral Blood (heparin, green or purple (EDTA) top tubes, 30-40mL)	X										
Bone Marrow/ Peripheral Blood Smears (Wright-Giemsa Stained)	X		X	X	X		X			X	
Karyotypes		X	X[14]	X[14]						X	Cytogenetic Laboratory
Rev. 3/15 Peripheral blood (SST, serum, 5mL tube) [6,8]					X[13]		X[10s]	X[10]	X[7]		LabConnect

	Pre-Registration[2]	Prior to Start of Treatment (Step 1)	Post Cycle 1 of Induction Chemotherapy (day 28)	Post Cycle 2 of Induction Chemotherapy (at time of count revcovery)	Prior to Randomization / Post Intensification	Post Cycle 1 of Blinatumomab	Post Initial 2 Cycles of Blinatumomab (Prior to Cycle 3 / Post Cycle 2 of Consolidation for those on Arm D)	Prior to Cycle 4 of Consolidation with Blinatumomab (Cycle 3 of Blinatumomab)	Post Consolidation / Prior to Start of Maintenance	Relapse[15]	Submit to:
	From patients who answer "Yes" to "I agree to participate in the laboratory research studies that are being done as part of this clinical trial."										
Peripheral Blood (heparin, green or purple EDTA top tubes, 30-40mL)			X	X	X		X			X	LTRL
	From patients who answer "Yes" to "I agree to provide additional specimens for research."										
Rev. 8/17 Peripheral Blood (red top tubes, 15-20mL)	X		X	X	X		X			X	LTRL
Buccal Rinse (preferred) or Swab[4]	X										

Rev. 7/14 1. Signed E1910 patient consents and HIPAA authorizations must be submitted to the ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL) prior to or at the time of submission of the pre-registration specimens to the LTRL.

Rev. 7/14 2. Pre-study (prior to cycle 1 induction) bone marrow and/or peripheral blood specimens must be submitted for centralized immunophenotyping.

Rev. 7/14 Rev. Add14 3. Bone marrow aspirates **must be submitted at the designated time points** for Minimal Residual Disease (MRD) assessments. Bone marrow will also be used as part of the optional defined laboratory research studies, per patient consent. The laboratory will accept any amount as long as it represents a first pull.

For the MRD assessments, aspirate from a separate bone marrow aspiration site must be submitted. **ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT ASPIRATES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE**.

Rev. 3/15 **MRD results will be reported to the submitting institution.**

Rev. 7/14 4. Buccal rinse (preferred) or swabs are strongly encouraged to be collected prior to the start of treatment, but can be collected at any other time during the study, if necessary.

Rev. Add14 5. For patients who were MRD positive at registration to Step 3 and patients who go to HSCT after only 1 cycle of blinatumomab, collect prior to HSCT.

Rev. 3/15 6. For patients receiving blinatumomab (Arm C).

7. Patients who test positive for neutralizing antibodies to blinatumomab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of blinatumomab. More frequent testing (e.g. every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Patients who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.
8. Kits are available for collection and shipment of the blood samples. See Section 10.4 for instructions.

Rev. 7/14
9. [Deleted in Addendum #2]
10. Collect immediately prior to the next dose of treatment.
11. Collect at time of count recovery.
12. Collect 2 weeks after completion of cycle 2 of blinatumomab and at the time of count recovery for non-blinatumomab.

Rev. 3/15
13. Collect post randomization, prior to start of treatment, for patients randomized to Arm C.

Rev. 8/17
14. Cytogenetic submission not necessary if prior study demonstrated normal karyotype (with at least 20 bone marrow metaphases analyzed). They should be repeated at each time point if abnormal at baseline or less than 20 bone marrow metaphases are analyzed.
15. First relapse sample in patients who achieve CR post induction (1 or 2) is mandatory. Subsequent relapse samples are also requested but not required.

Rev. 8/17
16. Bone marrow biopsy must be done at time of blood count recovery and not before.

8. Drug Formulation and Procurement

Availability

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account <https://ctepcore.nci.nih.gov/iam/> and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. These forms will be reviewed for accuracy and completeness during NCI cooperative group quality assurance audits.

Rev.6/16

NOTE: For commercial drugs, sites can prepare and administer the drugs according to their institutional SOP, if preferred.

Rev. 2/18

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/

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- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- **IB Coordinator**: IBCoordinator@mail.nih.gov

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8.1 Blinatumomab

8.1.1 Other Names

AMG103, MT103, Blincyto®

8.1.2 Classification

Bispecific T cell engaging antibody

8.1.3 Mode of Action

Through CD3 binding, blinatumomab recruits and engages T cells for redirected lysis of CD19-positive B cells, including those expressed with B-cell malignancies. T cells are bound by its anti-CD3 moiety, whereas B cells are bound by the anti-CD19 moiety. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T cell reaction. Treatment with blinatumomab is associated with a rapid depletion of peripheral B cells, accompanied by T cell activation and a transient increase in cytokines.

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8.1.4 Storage and Stability

Storage: Store intact vials of blinatumomab and IV solution stabilizer of blinatumomab refrigerated at 2° – 8°C (36°- 46°F), protect from light.

Stability: Shelf life stability studies of the intact vials of blinatumomab and stabilizer solution are on-going. The stability of the prepared IV solution in **preservative-free 0.9% NaCl** is 8 days when stored refrigerated at 2° to 8° C. The total storage and administration time must not exceed 8 days. Once at room temperature, discard the IV bag after 96 hours (4 days). The stability of the prepared IV solution in **Bacteriostatic 0.9% NaCl** is 14 days when stored refrigerated at 2° to 8° C. The total storage and administration time must not exceed 14 days. Once at room temperature, discard the IV bag after 168 hours (7 days).

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8.1.5 Dose Specifics

Rev. 3/15

Step 3 (Cycles 1 and 2):

28 mcg/day by continuous infusion for 28 days.

Consolidation (Cycles 4 and 6):

28 mcg/day by continuous infusion for 28 days.

8.1.6 How Supplied and Description

Description: Blinatumomab is a fusion protein composed of two single-chain antibodies (scFv), murine anti-CD19 scFv and murine anti-CD3 scFv.

Amgen provides and NCI/DCTD distributes blinatumomab and IV solution stabilizer for blinatumomab.

Rev. 3/15

1. Blinatumomab is available as a **38.5 mcg** preservative-free, white to off-white lyophilized powder for injection in 4 mL single-use vial. The agent is formulated with 3.68 mg citric acid monohydrate, 105 mg trehalose dihydrate, and 25.55 mg lysine hydrochloride, and 0.70 mg polysorbate 80, pH 7. The stopper of the vial is latex free.

2. **IV solution stabilizer for blinatumomab (NSC 773150) is not for reconstitution of blinatumomab.** The solution is available as a 10 mL single-use vial, preservative-free, clear, colorless-to-slightly yellow liquid solution. Each solution consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7. The stopper of the vial is latex free.

Rev. 7/14

8.1.7 Preparation

NOTE: Only trained staff may prepare blinatumomab IV solution. Sites' standard procedure for compounding blinatumomab must be in compliance with the USP <797> guidelines (ISO Class 5 or better). Use aseptic technique and prepare blinatumomab IV solution under a qualified laminar flow hood.

Rev. Add16

a. You need an **empty IV bag** that is made of Polyolefin/polyethylene, ethylene vinyl acetate (EVA) or PVC non-DEHP. The **IV Infusion sets** must be a PVC Non-DEHP with a low protein binding 0.2 µm inline filter.

NOTE: 168-hour (7-day) IV bag does NOT require an in-line filter.

Rev. 2/18

b. Next, reconstitute blinatumomab lyophilized powder:

a) Add 3 mL of Sterile Water for Injection (SWI) to the vial to yield 3.08 mL of blinatumomab at **a final concentration of 12.5 mcg/mL.**

b) Rotate the vial to dissolve all powder. Do not shake.

c) The stability of the reconstituted vial is 4 hours at room temperature (22° C to 27° C) or 24 hours refrigerated at 2° to 8° C.

Rev. Add14

c. Then, further dilute blinatumomab prior to administration: Steps to prepare solution are in sequential order. The IV solution stabilizer for blinatumomab **must be added into the 0.9% NaCl bag before adding blinatumomab.**

Rev. Add16

24-hour (1-day) IV bag (Inpatient): Infusion rate 10 mL/Hour	
Preparation: **Final volume is 270 mL** (steps are and must be in sequential order)	**Volume to be infused**
Step 1: Add the calculated preservative-free 0.9% NaCl volume into the approved empty IV bag Calculated 0.9% NaCl (mL): [total volume to be prepared (270 mL)] - [stabilizer solution volume (5.4 mL)] – [blinatumomab calculated dose volume (mL)] **Step 2:** Add 5.4 mL IV solution stabilizer into the preservative-free normal saline IV bag IV Stabilizer solution (5.4 mL): 0.02 x total volume to be prepared (270 mL) **Step 3:** Add the calculated blinatumomab dose volume into solution Blinatumomab calculated dose volume (per 270 mL bag): 24 hour dose (mcg) ÷ **Volume to be infused (240 mL)** x total volume to be prepared (270 mL) ÷ 12.5 mcg/mL of blinatumomab	**240 mL**
In summary, the total volume to be made is 270 mL of which patient will receive a total volume of 240 mL over 24 hours at 10 mL/hour rate and 30 mL* will remain in the IV-line set. You may also prepare a 24-hour IV bag for outpatient use but the overfill volume for the IV line infusion may be different and must be changed accordingly in the calculation.	

Rev. Add16

48-Hour (2-day) IV Bag (Outpatient): Infusion rate 5 mL/Hour	
Preparation: **Final volume is 250 mL** (steps are and must be in sequential order)	**Volume to be infused**
Step 1: Add the calculated volume of preservative-free 0.9% NaCl into approved empty IV bag 0.9% NaCl volume : [Total volume to be prepared (250 mL)] – [IV Stabilizer Solution volume (5 mL)] – [blinatumomab calculated dose volume (mL)] **Step 2:** Add 5 mL IV stabilizer solution into the preservative-free normal saline IV bag IV Stabilizer solution (5 mL): 0.02 x total volume to be prepared (250 mL) **Step 3:** Add the calculated dose volume of blinatumomab into solution Blinatumomab dose volume (per 250 mL bag): 48 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (250 mL) ÷ 12.5 mcg/mL of blinatumomab.	**240 mL**
In summary, the total volume to be made is 250 mL of which patient will receive 240 mL over 48 hours at 5 mL/hour rate and 10 mL* will remain in the IV line set.	

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72-Hour (3-day) IV Bag (Outpatient): Infusion rate 3.3 mL/Hour	
Preparation: **Final volume is 250 mL** (steps are and must be in sequential order)	**Volume to be infused**
Step 1. Add the calculated volume of preservative-free 0.9% NaCl into approved empty IV bag 0.9% NaCl volume : [Total volume to be prepared (250 mL)] – [IV Stabilizer Solution volume (5 mL)] – [blinatumomab calculated dose volume (mL)] **Step 2:** Add 5 mL IV stabilizer solution into the preservative-free normal saline IV bag IV Stabilizer solution (5 mL): 0.02 x total volume to be prepared (250 mL) **Step 3**: Add the calculated dose volume of blinatumomab into solution Blinatumomab dose volume (per 250 mL bag): 72 hour dose (mcg) ÷ volume to be infused (237.6 mL) x total volume to be prepared (250 mL) ÷ 12.5 mcg/mL of blinatumomab.	**237.6 mL**
In summary, the total volume to be made is 250 mL of which patient will receive 237.6 mL over 72 hours at 3.3 mL/hour rate and 12.4 mL* will remain in the IV-line set.	

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96-Hour (4-day) IV Bag (Outpatient): Infusion rate 2.5 mL/Hour	
Preparation: **Final volume is 250 mL** (steps are and must be in sequential order)	**Volume to be infused**
Step 1: Add the calculated volume of preservative-free 0.9% NaCl into approved empty IV bag 0.9% NaCl volume: [Total volume to be prepared (250 mL)] – [IV stabilizer solution volume (5 mL)] – [blinatumomab calculated dose volume (mL)] **Step 2:** Add 5 mL IV stabilizer solution into the preservative-free normal saline IV bag IV Stabilizer solution (5 mL): 0.02 x total volume to be prepared (250 mL) **Step 3:** Add the calculated dose volume of blinatumomab into solution Blinatumomab dose volume (per 250 mL bag): **96 hour dose** (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (250 mL) ÷ 12.5 mcg/mL of blinatumomab.	**240 mL**
In summary, the total volume to be made is 250 mL of which patient will receive 240 mL over 96 hours at 2.5 mL/hour infusion rate and 10 mL* will remain in the IV line set.	

168-hour (7-day) IV Bag (Outpatient) (Only for patients weighing ≥ 22 kg): Infusion rate 0.6mL/hour	
Preparation: **Final volume is 110 mL** (steps must be in sequential order) **(NOTE: 168-hour (7-day) IV bag does not require an in-line filter)**	**Volume to be infused**
Step 1. Add **90 mL Bacteriostatic 0.9% Sodium Chloride Injection, USP, preserved with 0.9% benzyl alcohol** into compatible empty IV bag. **Step 2:** Add 2.2 mL IV Solution Stabilizer (IVSS) into 90mL Bacteriostatic Sodium Chloride IV Solution bag. IV Stabilizer solution (2.2 mL): 0.02 x total volume to be prepared (110 mL) **Step 3**: Add the calculated dose volume of blinatumomab into solution Blinatumomab dose volume (per 110 mL bag): 168-hour dose (mcg) ÷ volume to be infused (100.8 mL) x total volume to be prepared (110 mL) ÷ 12.5 mcg/mL of blinatumomab. **Step 4:** q.s. with preservative-free 0.9% NaCl to final volume of 110 mL. Calculated volume of preservative-free 0.9% NaCl (mL): [Total volume to be prepared (110 mL)] – [Bacteriostatic Sodium Chloride volume (90 mL)] + [IV stabilizer solution volume (2.2 mL)] + [blinatumomab calculated dose volume (mL)]	**100.8 mL**
In summary, the total volume to be made is 110 mL of which patient will receive 100.8 mL over 168 hours at 0.6 mL/hour infusion rate and 9.2 mL will remain in the IV-line set.	

*Volume for the dead space of the IV line may be adjusted according to the size of the infusion IV line being used at each institution

a) Rotate IV bag to mix thoroughly the solution. Do not shake. Avoid foaming the IV bag.

b) Visually inspect for floating particles or discoloration of the IV solution. If that occurs, do not use the prepared solution.

c) Prime the IV line with the prepared IV solution before administering it to patient.

Infusion Pump:

- Use programmable pump that is approved by the appropriate regulatory authority for the country in which the subject is undergoing treatment.
- Pump alarm must be visual and auditory
- Pump must be lockable
- **Elastomeric pumps are NOT allowed**
- CADD Infusion pumps are allowed

IV bag label: Suggestion for the IV bag label

- Patient name and number
- Name of the drug
- Dose (mcg/day and volume/day)
- Infusion rate
- Expiration date and time

- CAUTION: NEW DRUG – Limited by United States law to investigational use.
- Bag number
- [Additional information may be provided on the label in accordance with state, local, and country pharmacy regulations.]

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8.1.8 **Route and Method of Administration: IV infusion**

Method of Administration: Use a central line to administer the IV solution. **Do not flush the IV line** as it will create an IV bolus to be administered into the patient.

NOTE: Infusion interruption: Record all interruption. Technical or logistical interruption must be as minimal as possible and re-start the infusion as soon as possible. If an interruption is longer than four hours, the re-start of the infusion must take place in the hospital under supervision of the investigator. Monitor patients for potential adverse events as described in the protocol and the Investigator Brochure.

8.1.9 Nursing/Patient Implications

Patient Care Implications: The effect of blinatumomab on fertility has not been evaluated. Blinatumomab is not recommended in pregnant women and in women of childbearing potential not using contraception. It is not known whether blinatumomab or its metabolites are excreted in human milk. Women are not allowed to breastfeed while receiving blinatumomab. Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reaction. Refer to protocol for specific recommendation. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances. Patients should not drive or operate dangerous machinery while receiving blinatumomab.

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The 7-day infusion with **Bacteriostatic 0.9% NaCl** preserved with benzyl alcohol is not allowed in patients weighing less than 22 Kg.

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8.2 Daunorubicin

8.2.1 Other Names

Daunomycin, Rubidomycin, Cerubidine.

8.2.2 Classification

Anthracycline antibiotic.

8.2.3 Mode of Action

Anthracycline mechanism of action results in a very tight binding of the drug to the DNA molecule. The ultimate effect is interference with nucleic acid synthesis, both RNA and DNA.

8.2.4 Storage and Stability

Intact vials are stored at room temperature and protected from direct sunlight. Reconstituted solutions are stable for 48 hours when

refrigerated and 24 hours at room temperature, when protected from sunlight.

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8.2.5 Dose Specifics:

Induction (Cycle 1) and Consolidation (Cycle 3):

25 mg/m^2 IV push, days 1, 8, 15, and 22

8.2.6 Preparation

Each 20 mg vial is reconstituted with 4 mL of sterile water to give a final concentration of 5 mg/mL. The desired dose is drawn into a syringe containing 10-15 mL of normal saline. Protect from sunlight.

8.2.7 Administration

10-15 minute intravenous infusion. Injection will be injected into the tubing of a rapidly flowing NS or D5W IV infusion. Do not give IM or SubQ.

8.2.8 Incompatibilities

Sodium heparin.

8.2.9 Availability

Commercially available in 20 mg glass vials of red colored lyophilized drug. Also available in 50 mg vials.

8.2.10 Side Effects

1. Hematologic: Myelosuppression (leukopenia with a nadir between 1-2 weeks).
2. Dermatologic: Rash; alopecia; chemical thrombophlebitis or local necrosis if extravasation occurs.
3. Gastrointestinal: Nausea, vomiting, commonly occurring one hour after a dose and lasting for several hours; diarrhea, stomatitis.
4. Cardiovascular: Arrhythmias, usually transient; congestive cardiomyopathy; maximum total (lifetime) dose of 500-600 mg/m² is recommended because of cumulative cardiotoxicity.
5. Renal: Red urine; not hematuria.
6. Other: Fever; transient elevations in serum bilirubin, AST, alkaline phosphatase.

8.2.11 Nursing Implications

1. Vesicant - avoid extravasation. Refer to extravasation protocol if inadvertent infiltration occurs.
2. Monitor CBC, platelet counts.
3. Advise patient of red coloration of urine.
4. Administer antiemetics as needed.

8.2.12 References

Von Hoff DD, Rozencweig M, Layard M, *et al.* Daunomycin-induced cardiotoxicity in children and adults: A review of 110 cases. Am J Med 1977; 62:200-208.

Yates J, Glidewell O, Wiernik P, *et al.* Cytosine arabinoside with daunorubicin or Adriamycin for therapy of acute myelocytic leukemia: A CALGB study. Blood 1982; 60:454-462.

8.3 Vincristine

NOTE: Refer to drug package insert for additional information.

NOTE: Potential drug interaction; i.e., Itraconazole should not be concomitantly administered with vincristine because it leads to severe neurotoxicity. Caution should be used with drug known to be CYP3A4/5 inhibitors or inducers.

8.3.1 Other Names

Oncovin®, Vincasar PFS®, VCR, leucocristine, LCR

8.3.2 Classification

Vinca alkaloid (tubulin inhibitor).

8.3.3 Mode of Action

Binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and interrupting mitosis.

8.3.4 Storage and Stability

Must be refrigerated.

8.3.5 Dose Specifics

Rev. 3/15 Induction (Cycle 1):

1.4 mg/m^2 IV, d1, 8, 15, 22 (cap each dose at 2mg total)

Rev. 3/15 Consolidation (Cycle 3):

1.4 mg/m^2 IV, d1, 8, 15, 22 (cap each dose at 2mg total)

Maintenance therapy:

Rev. 3/15 1.4 mg/m^2 IV every 3 months with prednisone (cap each dose at 2mg total)

8.3.6 Preparation

Doses for bolus injection are withdrawn from refrigerated vials without further dilution.

8.3.7 Administration

Intravenous bolus injection using extravasation precautions.

8.3.8 Incompatibilities

Furosemide, some in-line filters, polysiloxan containers used in portable delivery devices.

8.3.9 Compatibilities

Chemically stable in normal saline or 5% dextrose for at least four days, alone or mixed with doxorubicin (not used in this study) at room temperature in either glass or PVC containers. Also compatible with

bleomycin, cytarabine, fluorouracil, (not used in this study), methotrexate and metoclopramide.

8.3.10 Availability

Commercially available in a concentration of 1 mg/mL in 1, 2, and 5 mg vials; and 1 mg and 2 mg syringes (hyporets).

8.3.11 Side Effects

1. Hematologic: Leukopenia (mild and rare), thrombocytopenia (rare), anemia. Dysplastic marrow red cell precursors.
2. Dermatologic: Alopecia, skin and soft tissue damage if extravasated (subcutaneous injection of hyaluronidase and application of heat recommended by manufacturer to help disperse extravasated drug, rash).
3. Gastrointestinal: Nausea, vomiting (rare); constipation; abdominal pain and/or cramps; anorexia, diarrhea
4. Hepatic: Elevations of SGOT (AST), SGPT (ALT) which are usually mild and transient.
5. Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis); autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis); ataxia; myalgias; cortical blindness; headache; seizures. Fatal ascending paralysis follows intrathecal administration.
6. Pulmonary: Bronchospasm (more common when administered with mitomycin which is not used in this study).

8.4 Dexamethasone

NOTE: Refer to drug package insert for additional information.

8.4.1 Other Names

Decadron®, Hexadron®, Dexone®

8.4.2 Classification

Adrenal corticosteroid

8.4.3 Mode of Action

A potent synthetic glucocorticoid with anti-inflammatory, immunodepressant, antiemetic and antineoplastic activity. May form steroid-receptor complexes and alter mRNA and protein synthesis. Increases ribonuclease activity and decreases RNA concentration in lymphoid tissue.

8.4.4 Storage and Stability

Tablets are stored at room temperature.

Rev. 7/14

8.4.5 Dose Specifics

Rev. 3/15

Induction (Cycle 1) and, Consolidation (Cycle 3):

10 mg/m^2 days 1-7, and 15-21. Cap at 20 mg/day, days 1-7 only if age is greater than or equal to 55.

8.4.6 Preparation

Dexamethasone should always be taken after eating and never on an empty stomach.

8.4.7 Administration

Oral.

Rev. 3/15 A pill calendar will be provided to patients. See Appendix II

8.4.8 Availability

Commercially available as 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4 and 6 mg tablets and 0.1 mg/mL oral solution or syrup.

8.4.9 Side Effects

1. Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain, aggravation of peptic ulcer.
2. Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.
3. Genitourinary: Menstrual dysfunction.
4. Neurologic: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.
5. Cardiovascular: Fluid retention and edema, hypertension, thrombophlebitis (rare).
6. Ocular: Cataracts, increased intraocular pressure, exophthalmos.
7. Metabolic: Hyperglycemia, decreased glucose tolerance, aggrevation or precipitation of diabetes mellitus, adrenal suppression, Cushing syndrome, hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis with or without back pain; avascular necrosis of bone; serious infections including Herpes zoster, Varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of skin test reactions.

8.4.10 Nursing/Patient Implications

1. Always give oral dexamethasone with milk or food.
2. Observe for signs of hyperglycemia.
3. Observe for subtle signs of infection, such as lethargy, coldness to the touch, pain, etc.

8.5 Erwinase

NOTE: Refer to drug package insert for additional information.

NOTE: Erwinase will be substituted for patients who cannot take pegaspargase.

8.5.1 Other Names

Erwinase® (Erwinia derived)

8.5.2 Classification

Enzyme

8.5.3 Indication

Treatment of acute lymphocytic leukemia in pediatrics and adults

8.5.4 Mode of Action

Inhibits protein synthesis, including that of dihydrofolate reductase. Kills leukemic cells by depriving them of asparagines, which inhibits intracellular protein synthesis.

8.5.5 Storage and Stability

Intact vials are stored in refrigerator protected from light. The reconstituted solution drawn into syringe should be used within 6 hours

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8.5.6 Dose Specifics

Erwinia asparaginase 25,000 international units/m^2 (IU) IM or IV 3 times per week for 6 doses for each planned dose of pegaspargase.

8.5.7 Preparation

Reconstitute Erwinia formulation with 1 ml sodium chloride injection without preservative resulting in 10,000 IU/ml.

8.5.8 Incompatibilities

None known.

8.5.9 Compatibility

Erwinia derived stable with NSS

8.5.10 Availability

Erwinase® 10,000 IU vials

8.5.11 Side Effects

1. Hematologic: Prolonged thrombin and prothrombin times. Decreased fibrinogen and clotting factor concentration, particularly antithrombin III, resulting in thrombosis and/or pulmonary embolism.
2. Gastrointestinal: Nausea and vomiting uncommonly occur with IM use and can be readily controlled with standard antiemetics. Anorexia, abdominal cramps, weight loss, diarrhea, mucositis and malabsorption can each occur, but are rare with IM injection.
3. Hepatic: Liver enzyme elevations; depression of serum albumin, cholesterol and/or plasma fibrinogen.
4. Neurologic: EEG changes, depression, somnolence, lethargy, fatigue, convulsions and seizures (rare), coma (rare), headache, confusion, irritability, agitation, dizziness, hallucinations. All are uncommon or rare with IM use of doses prescribed in this protocol.

5. Hypersensitivity reactions: Urticarial eruptions, anaphylactoid reactions including laryngeal constriction, hypotension, diaphoresis, edema, asthma, and/or loss of consciousness. The most serious reactions are more likely to occur after several intravenous injections, but they may occur with the first injection and may occur with intramuscular injection. Leucovorin calcium is used if a hypersensitivity reaction to E. coli asparaginase occurs.
6. Renal: Azotemia, usually prerenal; rarely, severe renal failure.
7. Other: Pancreatitis, sometimes fulminant; hyperglycemia requiring insulin, chills, fever, hyperthermia (rare).
8. Adverse effects: Anaphylaxis and serious allergic reactions, serious thrombosis, pancreatitis, glucose intolerance, coagulopathy.

8.5.12 Nursing/Patient Implications

Rev.6/16

1. Use IM or IV route.
2. Limit IM volume at a single injection site to 2 mL.
3. Obtain baseline vital signs.
4. Have emergency medications such as parenteral diphenhydramine, epinephrine 1:1000, and parenteral hydrocortisone on hand.
5. Monitor liver and renal function, and blood glucose.
6. Assess for bleeding.
7. Assess for pancreatitis
8. Administer acetaminophen 30 – 60 minutes before injection.
9. Intradermal skin test if indicated.
10. Assess for anaphylaxis

8.6 Pegaspargase

NOTE: Refer to drug package insert for additional information.

8.6.1 Other Names

Pegaspargase (Oncaspar®)

8.6.2 Classification

Enzyme

8.6.3 Indication

Treatment of acute lymphocytic leukemia in pediatrics and adults

8.6.4 Mode of Action

Inhibits protein synthesis, including that of dihydrofolate reductase. Kills leukemic cells by depriving them of asparagines, which inhibits intracellular protein synthesis.

8.6.5 Storage and Stability

Intact vials are stored in refrigerator protected from light. The reconstituted solution drawn into syringe should be used within 6 hours

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8.6.6 Dose Specifics

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NOTE: Cap dose at 1 vial total (3750 IU).

Rev. 3/15

Induction (Cycle1):

pegaspargase 2,000 IU/m^2, IV or IM, d18, (omit if age ≥ 55 years)

Rev. 3/15

Induction (Cycle 2):

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pegaspargase 2,000 IU/m^2, IV or IM, d15 (omit if age ≥ 55 years)

Intensification:

pegaspargase 2,000 IU/m^2, IV or IM, d9 (1000 IU/m^2 if age ≥ 55 years)

Rev. 3/15

Consolidation (Cycle 1):

pegaspargase 2,000 IU/m^2, IV or IM d5 (1000 IU/m^2 if age ≥ 55 years)

Rev. 7/14

8.6.7 Preparation

Pegaspargase is available as liquid preparation

For IM administration, the injection solution drawn into a syringe should be used within 6 hours.

For IV administration, the manufacturer recommends diluting the dose of pegaspargase in 100 mL of dextrose 5% or sodium chloride 0.9% over one to two hours and giving in an already running line.

8.6.8 Incompatibilities

None known.

8.6.9 Availability

Oncaspar® 3750 IU/5 ml vial

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NOTE: For participating CCTG sites only, pegaspargase will be supplied by Baxalta/Shire and distributed by Bay Area Research Logistics (BARL). Please refer to http://www.ecog.org for the drug distribution request form.

8.6.10 Side Effects

1. Hematologic: Prolonged thrombin and prothrombin times. Decreased fibrinogen and clotting factor concentration, particularly antithrombin III, resulting in thrombosis and/or pulmonary embolism.
2. Gastrointestinal: Nausea and vomiting uncommonly occur with IM use and can be readily controlled with standard antiemetics. Anorexia, abdominal cramps, weight loss, diarrhea, mucositis and malabsorption can each occur, but are rare with IM injection.

3. Hepatic: Liver enzyme elevations; depression of serum albumin, cholesterol and/or plasma fibrinogen.
4. Neurologic: EEG changes, depression, somnolence, lethargy, fatigue, convulsions and seizures (rare), coma (rare), headache, confusion, irritability, agitation, dizziness, hallucinations. All are uncommon or rare with IM use of doses prescribed in this protocol.
5. Hypersensitivity reactions: Urticarial eruptions, anaphylactoid reactions including laryngeal constriction, hypotension, diaphoresis, edema, asthma, and/or loss of consciousness. The most serious reactions are more likely to occur after several intravenous injections, but they may occur with the first injection and may occur with intramuscular injection. Leucovorin calcium is used if a hypersensitivity reaction to E. coli asparaginase occurs.
6. Renal: Azotemia, usually prerenal; rarely, severe renal failure.

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7. Hyperlipidemia: elevated cholesterol and triglycerides.
8. Other: Pancreatitis, sometimes fulminant; hyperglycemia requiring insulin, chills, fever, hyperthermia (rare).
9. Adverse effects: Anaphylaxis and serious allergic reactions, serious thrombosis, pancreatitis, glucose intolerance, coagulopathy.

Rev. 7/14

8.6.11 Nursing/Patient Implications

1. Use IV or IM route (refer to Section 8.6.7 for administration instructions).
2. Limit IM volume at a single injection site to 2 mL.
3. Obtain baseline vital signs.
4. Have emergency medications such as parenteral diphenhydramine, epinephrine 1:1000, and parenteral hydrocortisone on hand.
5. Monitor liver and renal function, and blood glucose.
6. Assess for bleeding.
7. Assess for pancreatitis
8. Administer acetaminophen 30 – 60 minutes before injection.
9. Intradermal skin test if indicated.
10. Assess for anaphylaxis

8.7 Methotrexate

NOTE: Refer to drug package insert for additional information.

8.7.1 Other Names

Mexate®, Mexate-AQ®, Folex®, Folex PFS®, Abitrexate®, Rheumatrex®, Amethopterin, MTX

8.7.2 Classification

Antimetabolite

8.7.3 Mode of Action

Methotrexate inhibits the enzyme dihydrofolate reductase thereby blocking the conversion of folic acid to its active form, tetrahydrofolic acid. Inhibition of this enzyme reduces purine synthesis and the conversion of deoxyuridylate to thymidylate, which inhibits the synthesis of DNA, RNA and proteins.

8.7.4 Storage and Stability

Store at room temperature protected from light. Reconstituted solutions are stable at room temperature for at least one week. Solutions (50mg/100mL) in PVC bags of 5% dextrose may be frozen at -20ºC for at least 30 days and thawed in two minutes by microwave radiation. There is no loss of potency after five freeze-thaw cycles.

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8.7.5 Dose Specifics

Rev. 3/15

Induction cycles: (Cycle 1) 12.5 mg IT day 14 +/- 1 only

(Cycle 2) 12.5 mg IT days 1, 8, 15, and 22 +/- 1

Intensification: 3 g/m^2 IV days 1 and 8

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Consolidation: (Cycle 1, 2, 4) 12.5 mg IT day 1 +/- 1

(Cycle 3) 12.5 mg IT day 2 +/- 1

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Maintenance: 20 mg/m^2 PO or IV once per week.

12.5 mg IT day 1 +/- 3 every 3 months.

Rev. 8/17

NOTE: During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired. Once an adequate supply of preservative-free methotrexate has been obtained, the patient should be switched back to IT methotrexate in the following cycle.

Institutions without a sufficient supply of preservative-free methotrexate for high dose use can switch to using cytarabine, followed the next day by pegaspargase. The dose of cytarabine is 2 g/m^2 (or 1 g/m^2 if the patient age > 60) over 2 hours every 12 hours x four doses followed the next day by pegaspargase 1,000 IU/m^2 (500 IU/m^2 if patient age ≥ 55) IM or IV (recommended) (Maximum dose at one vial total; 3750 IU). This regimen is to be administered following the methotrexate schedule for Intensification – Arm B.

All other aspects of therapy and monitoring should be followed when using substitutions for methotrexate.

8.7.6 Preparation

Lyophilized sterile vials of 20, 50, 100 or 250 mg are reconstituted with sterile water, normal saline or 5% dextrose to a concentration no greater than 25 mg/mL. 1000 mg vials are reconstituted with 19.4 mL to provide a concentration of 50 mg/mL. Higher doses (> 100 mg) are usually further diluted with 100 mL or more of 0.45%-0.9% sodium chloride or 5% dextrose.

8.7.7 Administration

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In induction and consolidation, methotrexate is given by intrathecal injection. In intensification it is given as a 2-hr intravenous infusion. In maintenance methotrexate is given orally or intravenously and intrathecally.

8.7.8 Compatibilities

Methotrexate is compatible with sodium bicarbonate, cytarabine, cephalothin, mercaptopurine, vincristine sulfate, hydrocortisone, leucovorin, furosemide, and amino acids.

8.7.9 Incompatibilities

Incompatible in solution with bleomycin, fluorouracil, prednisolone sodium phosphate, droperidol, metoclopramide and ranitidine. Aspirin, probenecid, and nonsteroidal anti-inflammatory drugs may prolong methotrexate clearance and increase toxicity. They should not be given to patients receiving larger methotrexate doses during methotrexate infusion and for 48 hours afterward.

Rev. Add14

8.7.10 Availability

Commercially available as a lyophilized powder for injection (20, 50, 100, 250, and 1000 mg/vial), as a 25 mg/mL preservative-free isotonic solution for injection (50, 100, 200 and 250 mg vials), as a 2.5 mg/mL (5 mg vial) and 25 mg/mL (50 and 250 mg vials) preservative protected isotonic solution for injection, and as a 2.5, 7.5, 10, and 15 mg tablet.

8.7.11 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia (dose-related and more likely with prolonged drug exposure), anemia.
2. Dermatologic: Skin erythema and/or rash, sometimes pruritic; alopecia, photosensitivity, furunculosis, depigmentation or hyperpigmentation, acne, telangiectasia, skin desquamation and bullae formation, exfoliative dermatitis, folliculitis.
3. Gastrointestinal: Nausea and vomiting (uncommon with conventional doses; usually mild), stomatitis (dose and infusion-related, common), diarrhea, anorexia, hematemesis, melena.
4. Genitourinary: Renal dysfunction manifested by increased serum creatinine and/or hematuria), which is dose-related and more likely to occur in patients with already compromised renal function, dehydration, or on other nephrotoxic drugs.

5. Hepatic: Increased SGOT (AST), mild and transient; hepatic fibrosis and cirrhosis, more likely to occur in patients receiving long-term continuous or daily methotrexate treatment.
6. Neurologic: Encephalopathy, more commonly with multiple intrathecal doses and in patients who have received cranial irradiation; tiredness, weakness, confusion, ataxia, tremors, irritability, seizures, coma. Acute side effects of intrathecal methotrexate (not used in this protocol) may include dizziness, blurred vision, headache, back pain, nuchal rigidity, seizures, paralysis, and hemiparesis.
7. Allergic: Fever and chills; rash; urticaria; anaphylaxis.
8. Ocular: Conjunctivitis, excessive lacrimation, cortical blindness (rare, with high doses).
9. Pulmonary: Pneumonitis, pulmonary fibrosis, cough, dyspnea.
10. Other: Malaise, osteoporosis, avascular necrosis of bone (especially femoral head), hyperuricemia, reversible oligospermia, teratogenesis.

8.7.12 Nursing/Patient Implications

1. Administer antiemetics as indicated.
2. Monitor for hematologic toxicity.
3. Observe for stomatitis and diarrhea, offer symptomatic care if indicated.
4. Prior to the cytoreduction phase of this study proper functioning of the kidneys must be documented. During the cytoreduction phase proper hydration and alkalinization of the urine must be maintained.
5. Patient must use topical sunscreen when exposed to the sun.
6. The time of administration of methotrexate infusions and the duration of those infusions is critical in this study, especially during the cytoreduction phase. Methotrexate infusions must be carefully monitored, and should be controlled with an electronic pump.
7. Methotrexate infusions during the cytoreduction phase must be followed as indicated by leucovorin administration. The schedule and dose of both should be strictly adhered.

8.8 Cyclophosphamide

NOTE: Refer to drug package insert for additional information.

8.8.1 Other Names

Cytoxan®, Neosar®, CTX, CPM

8.8.2 Classification

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

8.8.3 Mode of Action

Cyclophosphamide metabolites are thought to disrupt cell division primarily by crosslinking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

8.8.4 Storage and Stability

Tablets and injectable powder are stored at room temperature 25°C (77°F). The temperature is not to exceed 30°C (90 F°). Reconstituted parenteral solutions are stable for 24 hours at room temperature for 6-14 days if refrigerated.[1-4]

8.8.5 Dose Specifics

Rev. 7/14, 3/15

Induction (Cycle 2):

1,000 mg/m^2 IV days 1 and 29 (Patients > 60 years give 800 mg/m^2 per dose)

Consolidation (Cycle 3):

650 mg/m^2 IV day 29

8.8.6 Preparation

Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 ml of sterile water, respectively, resulting in a solution of 20 mg/ml. Shake vials vigorously and warm slightly in lukewarm water to facilitate dissolution. The lyophilized form is more easily solubilized.

Rev. 7/14

Reconstituted solutions may be further diluted in D5W, D5W/NS, D5W/Ringer's Injection, Lactated Ringer's Injection, ½ NS or NS.

8.8.7 Administration

Rev. 3/15

May be given orally, IV push, or by IV infusion. A pill calendar will be provided to patients. See Appendix II

8.8.8 Compatibilities

Numerous compatibility studies have been published. For specific details refer to Handbook on Injectable Drugs by Lawrence A. Trissel[5].

8.8.9 Availability

Cyclophosphamide is commercially available as 25 mg and 50 mg tablets and for parenteral injection as 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.

8.8.10 Side Effects

Side effects vary significantly based on the specific dose and duration of cyclophosphamide.

Incidence more frequent (> 5%):

Anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills); Thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising; black tarry stools; blood in

urine or stools; pinpoint red spots on skin). Nadir counts usually occur 7 to 12 days after administration and recovery usually compete by day 17 to 21.

Alopecia

Anorexia, nausea and vomiting

Gonadal suppression (azoospermia, missed menstrual periods) resulting in infertility.

Return of normal gonadal function and fertility occurs with time in many younger men and women.[3]

Hemorrhagic cystitis[3,8]

Incidence less frequent (1-5%):

Stomatitis

Incidence rare (1%):

Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat), flushing or redness of face, diarrhea , skin rash, pneumonitis or interstitial pulmonary fibrosis, syndrome of inappropriate antidiuretic hormone (SIADH), chemical phlebitis (redness, swelling or pain at site of injection), secondary malignancies, blurred vision, cardiac toxicity presenting as congestive heart failure, hemorrhagic myocarditis, myocardial necrosis, and pericarditis (seen with high dose regimens used with bone marrow transplantation).

8.8.11 Drug Interactions

Digoxin: Several studies conducted in lymphoma patients receiving combination chemotherapy including cyclophosphamide revealed a 20–50% reduction in digoxin absorption when digoxin tablets were administered. When digoxin capsules were administered no significant decrease in digoxin absorption occurred. To avoid decreased serum digoxin levels the use of digoxin in liquid form (liquid or capsules containing liquid digoxin) instead of tablets is recommended. [3,10-11]

Pentostatin: Two case reports describe fatal cardiac toxicity in patients receiving CTX 6.4 g/m^2 over 4 days and pentostatin 4 mg/m^2 over 4 hours on day 3. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended. [3,7]

Succinylcholine: Cyclophosphamide may prolong the effects of succinylcholine by irreversibly inhibiting the enzyme pseudocholinesterase. Limited clinical observations and in vitro studies suggest that prolonged apnea might result when succinlycholine is administered to some patients also receiving cyclophosphamide. Management options include avoiding concurrent therapy or if concurrent therapy cannot be avoided, to monitor for prolonged succinlycholine effect in patients receiving both drugs. If cyclophosphamide has been administered within 10 days of succinylcholine, extreme caution should be used after succinylcholine

administration. The anesthesiologist should be informed of the potential for succinylchoine-induced apnea and appropriate precautions and monitoring should be implemented. [3,10,11]

Trastuzumab: In early clinical trials the concurrent administration of cyclophosphamide and trastuzumab increased the incidence and severity of cardiac dysfunction. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended. [3,12]

8.8.12 Nursing Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with an absolute neutrophil count less than 500 cells/mm3 and increased risk of bleeding with platelet counts less than 20,000 cells/ mm3. Advise patients to call the clinic if they develop a fever above 101°F or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters above normal intake for 72 hours after administration. Instruct patients to void more frequently to minimize occurrence of hemorrhagic cystitis. For high-dose therapy MESNA may be used.
4. Premedicate with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.8.13 References

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2. Cytoxan package insert, Princeton, NJ: Mead Johnson Oncology Products 1998; July
3. Micromedex Inc. Vol. 101; 1999.
4. USPDI Volume1 1999:1128-1134.
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7. Gryn et.al., Pentostatin increases the acute toxicity of high dose cyclophosphamide. Bone Marrow Transplantation 1993;12:217-220.
8. Pedersen-Bjergaard J, Ersboll J, Sorenson HM. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non- Hodgkin’s lymphoma. Ann Intern Med 1985;103:195-200.

9. Stillwell TJ, Benson RJ. Cyclophosphamide-induced hemorrhagic cyctitis: A review of 100 patients. Cancer 1988;61:451-457.
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11. Hansten PD, ed. Drug interactions analysis and management. Applied Therapeutics, Inc., Vancouver, WA: 1998:185-186.
12. Trastuzumab package insert, South San Francisco, CA: Genentech, Inc. 1998;September Date/Reviewer: July 1999/Robert K. Sylvester, Pharm.D. (701) 234-5154

8.9 Cytarabine

NOTE: Refer to drug package insert for additional information.

8.9.1 Other Names

Cytosar-U™, Ara-C, Arabinosyl, cytosine arabinoside.

8.9.2 Classification

Antimetabolite.

8.9.3 Mode of Action

Converted to cytarabine triphosphate (Ara-CTP), a competitive inhibitor of DNA polymerase. The drug is also incorporated into cellular DNA and RNA. It is active against cells in S-phase and is considered to be phase specific.

8.9.4 Storage and Stability

The dry powder is stored at room temperature. Solutions reconstituted with sterile water without preservative should be used immediately; solutions reconstituted with Bacteriostatic of Water are stable up to 48 hours at controlled room temperature (15° to 30°C). Solutions with a slight haze should be discarded.

8.9.5 Dose Specifics

Rev. 3/15

Induction (Cycle 1): 70 mg IT day 1

(Cycle 2): 75 mg/m^2 IV days 1-4, 8-11, 29-32, 36-39

Consolidation (Cycle 1, 2, 4, 5): 75 mg/m^2 IV days 1-5

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(Cycle 3): 75 mg/m^2 IV days 30-33, 37-40

8.9.6 Preparation

For IV use, reconstitute the 100 mg vial with 5 mL bacteriostatic water for injection to achieve a concentration of 20 mg/mL. Add 10 mL of bacteriostatic water to the 500 mg vial to achieve a final concentration of 50 mg/mL. Add 10 and 20 mL of bacteriostatic water to the 1 and 2 gm vials respectively to achieve a final concentration of 100 mg/mL. For subcutaneous use, reconstitute the powder with sterile water or saline to a concentration of 50-100 mg/mL. For IT use, mix with lactated Ringer's solution or normal saline without preservatives.

8.9.7 Administration

IV push, IV continuous infusion, subcutaneous, or IT. Cytarabine is not absorbed when given orally.

8.9.8 Incompatibilities

Possible interaction with fluorouracil.

8.9.9 Compatibilities

Cytarabine (0.25 mg/mL), daunorubicin (0.03 mg/mL) and etoposide (0.4 mg/mL) are stable in D5/0.45% NaCl for 72 hours at room temperature. Cytarabine is also compatible with sodium chloride, potassium chloride, calcium, and magnesium sulfate.

8.9.10 Availability

Commercially available in 100 mg, 500 mg, 1 gm, and 2 gm vials.

8.9.11 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, anemia, and phlebitis. Nadir occurs in 5-7 days with recovery in 2-3 weeks.
2. Dermatologic: Rash, alopecia.
3. Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia, mucositis, anorexia.
4. Hepatic: Transient increase in liver enzymes.
5. Renal: Urinary retention.
6. Other: Flu-like syndrome, fever. Profound hyperuricemia may occur in leukemia patients with high white blood counts. Conjunctivitis, dizziness, shortness of breath, headache, urticaria, pruritis, abdominal pain, pericarditis.
7. After intrathecal administration, the most common side effects are nausea, vomiting, fever, and headache, usually mild and self-limiting. Meningism, paresthesia, paraplegia, seizures, blindness, necrotizing encephalopathy have occurred.

8.10 Mercaptopurine

NOTE: Refer to drug package insert for additional information.

8.10.1 Other Names

Purinethol®, 6-MP

8.10.2 Classification

Antimetabolite

8.10.3 Mode of Action

Mercaptopurine is converted intracellularly to the ribonucleotide derivative 6-MP ribose phosphate (6-thioinosinic acid), which may be incorporated into RNA, thus inhibiting its effects. It also blocks several steps in the synthesis of purines.

8.10.4 Storage and Stability

Tablets are stored at room temperature.

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Rev. 7/14

8.10.5 Dose Specifics

Take at bedtime on an empty stomach 1 hour before or 2 hours after food and/or milk products. Round the dose to the nearest 25 mg half-tablet.

Rev. 8/17

NOTE: If tablets may not be split into 25 mg increments, calculate the daily dose, round to the nearest 50 mg tablet size, and determine the number of tablets needed per week and administer tablets accordingly.

Rev. 3/15

Induction (Cycle 2): 60 mg/m^2 orally days 1-14, 29-42

Consolidation (Cycle 3): 60 mg/m^2 PO days 29-42

Maintenance 75 mg/m^2 PO/day continuously.

8.10.6 Preparation and Administration

Tablets are given orally. The investigational parenteral form of this agent is not used in this study. A pill calendar will be provided to patients. See Appendix II

Rev. 3/15

8.10.7 Incompatibilities

When administered with allopurinol, the dose of mercaptopurine is reduced to 25%-30% of the usual dose. Allopurinol inhibits xanthine oxidase, which metabolizes mercaptopurine.

8.10.8 Availability

Commercially available as 50 mg tablets.

8.10.9 Side Effects

Hematologic: Leukopenia, thrombocytopenia, anemia

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Dermatologic: Hyperpigmentation (rare), rash (rare)

Gastrointestinal: Nausea, vomiting, anorexia, abdominal pain, mucositis (all uncommon)

Hepatic: Jaundice, elevated hepatic enzymes, cholestasis, ascites, hepatic encephalopathy associated with hepatic necrosis and fibrosis. Variable onset, usually in 1-2 months. Deaths have occurred. All more frequently associated with doses over 2.5 mg/kg/day.

Other: Fever, headache

8.10.10 Nursing/Patient Implications

1. Monitor CBC, platelet count, liver function tests.
2. Monitor for GI toxicities and drug fever, and treat symptomatically.
3. The parenteral preparation is a vesicant (not used in this study).
4. Administer in evening on empty stomach (at least 1 hour before or 2 hours after food or drink except water).
5. Maintain adequate hydration to prevent hyperuricemia

8.11 Etoposide

NOTE: Refer to drug package insert for additional information.

8.11.1 Other Names

VP-16, VePesidÒ, VP-16-213, EPEG, epipodophyllotoxin, NSC #141540

8.11.2 Classification

Podophyllotoxin derivative.

8.11.3 Mode of Action

The exact mechanism(s) of action of etoposide is not fully understood; it is thought to produce its antineoplastic effects by inhibiting or altering DNA synthesis. Single-stranded and double-stranded DNA breaks may result from etoposide's inhibition of the intranuclear enzyme topoisomerase II, endonuclease activation or formation of a free-radical metabolite. In vitro data suggest that it has phase-specific activity inducing G2 arrest resulting in cell death in the G2 and late S phases.[1,2]

8.11.4 Storage and Stability

Parenteral: Unopened vials of etoposide injection are stable for 18 months at room temperature (59-86º F). Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/ml are stable for 96 and 242 to 483 hours respectively, at room temperature (25º C) under normal room fluorescent light in both glass and plastic containers.2 Bristol-Myers in-house data indicate that etoposide may be stable in 5% dextrose or normal saline at the following more concentrated solutions for decreasingly shorter times (0.6 mg/mL for 8 hours, 1 mg/mL for 2 hours, 2 mg/ml for 30 minutes). 10 Capsules: Capsules must be stored under refrigeration 2º to 4º C (36º to 46º F). The capsules are stable for 24 months when stored according to these recommendations.[3]

8.11.5 Dose Specifics

Rev. 3/15

Consolidation (Cycle 1, 2, 4, 5): 100 mg/m^2 IV days 1-5

8.11.6 Preparation

The desired dose is usually diluted to a concentration of < 0.4 mg/ml in normal saline or 5% dextrose. More concentrated solutions may be used but have shorter stability (and may precipitate).

Rev. 3/15

8.11.7 Administration

Slow IV infusion over at least 30-60 minutes to prevent hypotension.

8.11.8 Compatibilities

At concentrations of 400 mcg/mL etoposide is compatible with cisplatin 200 mcg/ml in NS, at room temperature for 5 days.

At concentrations of 200 mcg/mL or 400 mcg/mL etoposide is compatible with cisplatin 200, mannitol 18.75 g/L, and potassium

chloride 20 mEq/L in NS, should be protected from light and used within 8 hours.

At concentrations of 200 mcg/mL or 400 mcg/mL etoposide is compatible with cisplatin 200, mannitol 18.75 g/L, and potassium chloride 20 mEq/L in 5% Dextrose and 0.45% NS for 24 hours.

Potential drug-device interaction during use of undiluted etoposide:

There is a potential drug-device interaction regarding undiluted etoposide and some plastics. Cracking of venting pins and line connectors containing a hard plastic called ABS (a polymer produced from acrylonitrile, butadiene and styrene) has been reported.[12] When administering undiluted etoposide in an investigational setting you are recommended to contact the manufacturer of the plastic device coming in contact with undiluted etoposide, in order to determine (a) the type of plastic used in the device and (b) compatibility with the various solvents found in etoposide injection [PEG 300; alcohol (30.5% by volume); benzyl alcohol; Tween 80; polysorbate 80].[13]

8.11.9 Availability

Rev. 8/17

Commercially available for injection in the concentration of 20 mg/mL in 5, 7.5, 25, and 50 Ml multiple dose vials.

8.11.10 Side Effects

Incidence more frequent (>5%):

Alopecia, anorexia, nausea and vomiting, anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills), thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising, black tarry stools, blood in urine or stools, pinpoint red spots on skin). Nadir counts usually occur 7 to 16 days after administration and recovery usually complete by day 20.

Incidence less frequent (1-5%):

Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat); stomatitis; diarrhea, secondary leukemia (acute myeloid leukemia) [15,16]

Incidence rare (< 1%):

Chemical phlebitis, neurotoxicity, skin rash or itching

8.11.11 Nursing Implications

1. Monitor CBC, platelet count
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Infuse drug over at least 30 minutes. A more rapid infusion may cause hypotension.
4. Observe for possible phlebitis at injection site or burning pain with infusion.
5. Administer antiemetics as indicated.

8.11.12 References

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3. Etoposide package insert, Princeton, NJ; Bristol Laboratories Oncology Products 1997; March.
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13. Personal communication. Bristol-Myers Squibb Oncology; May 13, 1998.
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8.12 Leucovorin Calcium

8.12.1 Other Names

Leucovorin®, Wellcovorin®, folinic acid, 5-formyltetrahydrofolate, Citrovorum factor

8.12.2 Classification

Tetrahydrofolic acid derivative

8.12.3 Mode of Action

Leucovorin calcium acts as a cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin calcium does not require dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin calcium.

8.12.4 Storage and Stability

All dosage forms are stored at room temperature. The reconstituted parenteral solution (10 mg/mL) is stable for at least seven days at room temperature. Concentrations of 0.5-0.9 mg/mL are only stable for approximately 24 hours at room temperature. The oral solution (1 mg/mL) is stable for 14 days refrigerated and seven days at room temperature.

8.12.5 Dose specifics

Intensification 10 mg/m^2 IV every 6 hours x 4 doses beginning 22-24 hours after completion of MTX, then 10 mg/m^2 PO every 6 hours x 72 hours.

8.12.6 Preparation

The 50 and 100 mg vials for injection are reconstituted with 5 and 10 mL of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/mL solution. The 350 mg vial is reconstituted with 17 mL of sterile water resulting in a 20 mg/mL solution. The 60 mg bottle for oral solution is reconstituted with 60 mL of aromatic elixir provided, resulting in a 1 mg/mL oral solution.

Rev. 3/15

8.12.7 Administration

Leucovorin calcium is given intravenously or orally. The former is preferred after high-dose methotrexate. A pill calendar will be provided to patients. See Appendix II

8.12.8 Compatibilities

Leucovorin calcium can be reconstituted in normal saline, 5% dextrose, 10% dextrose, Ringer's or lactated Ringer's solutions. It may be admixed with certain fluoropyrimidines for other protocols.

8.12.9 Availability

Commercially available as tablets (5, 10, 15, 25 mg), cryodessicated powder for oral solution, and in parenteral formulations (ampoules of 3 and 5 mg; vials of 50, 100, and 350 mg).

8.12.10 Side Effects

1. Hematologic: Thrombocytosis
2. Dermatologic: Skin rash
3. Gastrointestinal: Nausea, stomach discomfort, diarrhea

4. Allergic: Hives, pruritis, skin rash
5. Pulmonary: Wheezing
6. Other: Headache. May potentiate side effects of fluoropyrimidines

8.12.11 Nursing/Patient Implications

1. Observe for sensitization reactions.
2. Dose timing is critical. The schedule must be understood thoroughly.

Rev. 7/14

8.13 Prednisone

8.13.1 Other Names

Deltasone, Orasone, Medicorten, Panasol-S, Liquid-Pred, others

8.13.2 Classification

Adrenal corticosteroid.

8.13.3 Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.13.4 Storage and Stability

The drug is stored at room temperature in a dry place. Refer to the package insert from the manufacturer for storage specifics.

8.13.5 Dose Specifics

Maintenance therapy: 60 mg/m^2 for 5 days by mouth taken with meals every 3 months with vincristine

8.13.6 Administration

Prednisone is taken orally (with food or a meal). A pill calendar will be provided to patients. See Appendix II.

8.13.7 Availability

Commercially available in 1, 2.5, 5, 10, 20, 25 and 50 mg tablets. Also available as a 1 mg/ml oral solution or syrup and as a 5 mg/mL oral solution.

8.13.8 Side Effects

1. Gastrointestinal: Nausea, vomiting, anorexia; increased appetite and weight gain; peptic ulceration.
2. Dermatologic: Rash; skin atrophy; facial hair growth, acne, facial erythema; ecchymoses.
3. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities), urinary frequency.

4. Neurologic: Insomnia; muscle weakness; euphoria, psychosis, depression; headache, vertigo, seizures.
5. Cardiovascular: Fluid retention and edema; hypertension.
6. Ocular: Cataracts; increased intraocular pressure; exophthalmos.
7. Metabolic: Hyperglycemia; decreased glucose tolerance; aggravation or precipitation of diabetes mellitus; adrenal suppression; Cushingoid features; hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis (and resulting back pain); serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

8.13.9 Nursing Implications

1. Instruct patients to take prednisone after meals. Should not be taken too close to bedtime to avoid insomnia. A mild sedative may be required.
2. GI symptoms should be treated symptomatically.
3. Monitor blood glucose levels.
4. Educate patient concerning potential mood swings.

NOTE: Please refer to the commercially-available package labeling for more information.

8.13.10 References

Pickup ME: Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet 4:111-128, 1979.

The Boston Collaborative Drug Surveillance Program: Acute reactions to prednisone in relation to dosage. J Clin Pharmacol 13:694-698, 1972.

Ling MHM, Perry PJ, Tsuang MT: Side effects of corticosteroid therapy: Psychiatric aspects. Arch Gen Psychiatry 38:471-477, 1981.

Rev. 3/15

8.14 <u>Rasburicase</u>

NOTE: Refer to drug package insert for additional information.

8.14.1 Other Names

Elitek®

8.14.2 Classification

Recombinant enzyme, urate-oxidase

8.14.3 Mode of Action

Rasburicase is a recombinant urate-oxidase enzyme, which converts uric acid to allantoin. Allantoin is an inactive and highly soluble metabolite of uric acid.

8.14.4 Storage and Stability

Prior to reconstitution, store with diluent at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Reconstituted solution may be stored up to 24 hours at 2°C to 8°C (36°F to 46°F).

8.14.5 Dose Specifics

Rasburicase 0.1 to 0.2 mg/kg/day IV over 30 minutes for 1-3 days or up to five days (or a flat dose of 3 or 6 mg daily)

8.14.6 Preparation

Reconsitute with the provided diluent. Use 1ml of diluent for the 1.5mg vial and 5ml diluent for the 7.5mg vial. Mix by gently swirling; do not shake. Total dose should be further diluted in NS to a final volume of 50ml.

8.14.7 Administration

IV infusion over 30 minutes

8.14.8 Compatibilities

NS. No known drug compatibilities.

8.14.9 Availability

Rasburicase is commercially available as a 1.5 and 7.5mg vial.

8.14.10 Side Effects

Incidence >10%:

Cardiovascular: Peripheral edema (≤50%), fluid overload (≤12%)

Central nervous system: Fever (46%; serious: 5%), headache (26%), anxiety (≤24%)

Dermatologic: Rash (13%; serious: 1%)

Endocrine & metabolic: Hypophosphatemia (≤17%)

Gastrointestinal: Vomiting (50%), nausea (27%), abdominal pain (20%), constipation (20%), diarrhea (20%), mucositis (15%; serious: 2%)

Hepatic: Hyperbilirubinemia (≤16%), ALT increased (≤11%)

Respiratory: Pharyngolaryngeal pain (≤14%)

Miscellaneous: Antibody formation (healthy volunteers: 61% to 64%; patients with malignancies: 11%), sepsis (≤12%; serious: 3% to 5%)

1% to 10%:

Cardiovascular: Ischemic coronary disorder, supraventricular arrhythmia

Endocrine & metabolic: Hyperphosphatemia (≤ 10%)

Gastrointestinal: Abdominal/gastrointestinal infection

Hematologic: Neutropenic fever (serious: 4%), neutropenia (serious: 2%)

Respiratory: Respiratory distress (serious: 3%), pulmonary hemorrhage, respiratory failure

Miscellaneous: Hypersensitivity (≤ 4%)

< 1% (Limited to important or life-threatening): Acute renal failure, anaphylaxis, arrhythmia, cardiac arrest, cardiac failure, cellulitis, cerebrovascular disorder, chest pain, cyanosis, dehydration, hemolysis, hemorrhage, hot flashes, ileus, infection, intestinal obstruction, liver enzymes increased, methemoglobinemia, MI, pancytopenia, paresthesia, pneumonia, pulmonary edema, pulmonary hypertension, retinal hemorrhage, rigors, seizure, thrombosis, thrombophlebitis

8.14.11 Drug Interactions

No known significant drug interactions

Rev. 8/17

8.15 Rituximab

8.15.1 Other Names

IDEC-C2B8, Rituxan®

8.15.2 Classification

Antibody.

8.15.3 Mode of Action

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells. It binds with high affinity to CD20-positive cells, performs human effector functions *in vitro*, and depletes B cells *in vivo*. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro.* The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.15.4 Storage and Stability

Intact vials should be stored under refrigeration (2°-8°C). Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

8.15.5 Dose Specifics

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Administer if CD20 positive (do not administer if patient is CD20 negative); optional and not required to give if not available or desired. If patient is CD20 positive and positive for hepatitis B, and rituximab treatment is planned, prophylaxe the patient with lamivudine, entecavir, or tenofovir as per figure 1 of recently published guidelines[78].

Induction (Cycles 1, 2): 375mg/m^2 IV on Day 8 and 15

Consolidation (Cycles 1, 2, 4 (Arm D only), and 5 (Arm C Only)): 375mg/m^2 IV on Day 5

Consolidation (Cycle 3): 375mg/m^2 IV on Day 8

8.15.6 Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

8.15.7 Administration

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Rituximab is administered intravenously. An in-line filter is not required. The initial rate is 50 mg/hr for the first hour. If no toxicity is seen, the rate may be escalated gradually in 50 mg/hour increments at 30-minute intervals to a maximum of 400mg/hr. If the first dose is well tolerated, the initial rate for subsequent dose is 100mg/hr, increased gradually in 100 mg/hr increments at 30-minute intervals, not to exceed 400 mg/hr. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects should be evaluated. If the symptoms improve, the infusion is continued initially at one-half the previous rate. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued. Oral pre-medication (2 tablets, 650 to 1000 mg, of acetaminophen and 25 to 50 mg diphenhydramine) will be administered 30 to 60 minutes prior to starting each infusion of rituximab. The patient should be treated according to the best available local practices and procedures.

NOTE: In addition, alternative rituximab infusion rates (i.e., “rapid rituximab infusion”) can be used per institutional guidelines as long as the total number of milligrams of rituximab is the same and that “rapid infusion” is not administered with the patients first rituximab cycle. Further, a rituximab infusion time should never be given over <u>less than</u> 90 minutes (common infusion time for “rapid infusion” is 20% of the bag volume over 30 minutes, and then 80% of the remaining bag volume over 60 mintues).

8.15.8 Availability

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL. Please refer to the agent’s package insert for additional information.

8.15.9 Side Effects

<u>Likely side effects:</u>

Chills, fever; Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing. Lowered white blood cell count.

Less likely side effects:

Lowered red blood cell count (may cause anemia, weakness, fatigue), Fever associated with dangerously low levels of a type of white blood cell (neutrophils), Heart attack caused by a blockage of a blood vessel supplying part of the heart, Fast heartbeat, Belly pain, Diarrhea, Nausea or the urge to vomit, Vomiting, Swelling of the arms and/or legs, Fatigue or tiredness, Pain, Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing; Allergic reaction to other medications, injected proteins, or antisera (blood product) used to treat certain medical conditions (such as an infectious or poisonous substance), Infection, Awakening of viruses which have been latent/dormant, Infection in HIV positive patients, Lowered platelet count that might interfere with clotting (may make you more likely to bruise or bleed), Decrease in the total number of white blood cells (leukocytes), Increased blood sugar level, Decreased blood level of calcium, Decreased blood level of potassium, Joint pain, Back pain, Muscle pain, Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness), Headache or head pain, Abnormal drowsiness or sluggishness, an unusual lack of energy, Convulsion or seizure, Sudden or traumatic injury to the kidney, Stuffy or runny nose, sneezing, Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath, Cough, Shortness of breath, Decrease in the oxygen supply to a tissue, Inflammation of the lungs that may cause difficulty breathing and can be life-threatening, Sore throat, Excess sweating, Itching, Skin rash, Swelling of body tissue underneath the skin, Hives, Sudden reddening of the face and/or neck, High blood pressure, Low blood pressure. Rare but serious side effects include: Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness. Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure. Disease affecting brain tissue, caused by the JC virus. Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs. Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue. Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer). Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer).

8.15.10 Nursing Implications

1. Monitor blood pressure, pulse, respiration, and temperature every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued.

2. Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.
3. Monitor and alter infusion rates in the presence of toxicities.
4. Carriers of hepatitis B virus should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout study participation.
5. Due to the risks of bowel obstruction and bowel perforation, patients should be monitored for complaints of abdominal pain, especially early in the course of treatment.
6. Patients with concurrent RA should be monitored throughout the infusion and rituximab ahould be discontinued in the event of a serious or life-threatening cardiac event.

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9. Statistical Considerations

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Rev. Add14

9.1 Original Design Overview and Primary Endpoint

In the original design, patients with BCR/ABL-negative B cell precursor ALL aged 30-70 will be randomized to receive either blinatumomab or no blinatumomab after achieving CR/CRi and receiving intensification treatment, stratified by MRD status (positive vs. negative), age (30-54 vs. ≥ 55 years), CD20+ status (positive vs. negative), rituximab use (yes vs. no), and whether patients intend to receive HSCT or not. Patients will not be randomized until they have completed intensification and the bone marrow MRD sample has been analyzed. If there is no bone marrow sample available, peripheral blood (PB) will be analyzed for MRD. Patient with MRD positive status based on the PB sample will also be randomized. After randomization, suitable patients may then proceed to myeloablative or reduced intensity HSCT at investigator discretion. The primary objectives of this phase III study are to compare the OS in patients who received blinatumomab in conjunction with chemotherapy to that of patients who received chemotherapy alone in MRD+ subset, MRD- subset, and the overall population. OS is defined as the time between randomization and death from any cause. Patients last known to be alive at the time of an analysis will be censored. To control the overall one-sided type I error at 0.025, the OS comparison in the MRD+ subset will be tested first at one-sided type I error of 0.02. If it is significant, the OS comparison in MRD- subset will be tested at one-sided type I error of 0.025. Otherwise, the OS comparison in overall population will be tested at one-sided type I error of 0.005. (See Freidlin et al.[47])

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9.2 Summary of Design Changes and Rationale

On March 29, 2018, the U.S. Food and Drug Administration granted accelerated approval to blinatumomab to treat adults and children with B-cell precursor ALL who are in remission but still MRD+. Considering the current high non-compliance rate of the MRD+ patients in the no blinatumomab arm and anticipating that the rate will go higher after the FDA approval, to answer the blinatumomab question in MRD+ patients as originally designed will be infeasible. The study team decided to discontinue randomizing MRD+ patients. From this amendment, all MRD+ patients will be registered at Step 3 to receive blinatumomab directly. Patients who are MRD- after achieving CR/CRi and receiving intensification treatment will continue to be randomized to receive either blinatumomab or no blinatumomab.

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9.3 Sample Size and Primary Objective

In the revised design, the primary objective of the study will be to compare the OS in patients who received blinatumomab in conjunction with chemotherapy to that of patients who received chemotherapy alone in MRD- patients. As a secondary objective, the OS of those patients who are MRD+ at step 3 randomization/registration and then convert to MRD- after 2 cycles of blinatumomab will be compared to those patients who are MRD- at randomization and remain MRD- after 2 cycles of blinatumomab or consolidation chemotherapy.

We plan to enter a total of 488 BCR/ABL-negative B cell precursor ALL patients aged 30-70 in this study. Based on current data, we assume that a total of 190

(39% of the 488) patients will be MRD- and be randomized to receive either blinatumomab or no blinatumomab. Based on E2993, we assume the survival function of this ALL patient population can be described by a cure rate model. For MRD- patients, we assume a 35% long-term cure rate and 13-month median OS in the non-cured group in the control arm. Adjusted for sequential monitoring, with 190 MRD- patients, the study will have 80% power to detect 45% reduction in hazard rate in the blinatumomab arm relative to the no blinatumomab arm, using one-sided log rank test at the significance level of 0.025 and assuming 2 years of follow-up, which is equivalent to detecting an improvement in the 3-year OS rate from 45% to 64%. The number of events needed is 94.

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The final analyses will be done when the full information for MRD- patients (94 events) is reached. Estimates of OS, including medians and confidence intervals, will be calculated using the Kaplan-Meier method. Comparison of OS between treatment arms will be conducted using the one-sided stratified log-rank test with, age, CD20 status, rituximab use, and whether patients intend to receive HSCT or not as stratification factors at overall one-sided type I error of 0.025. The primary comparisons of OS will be based on the intention-to-treat (ITT) principle, including all patients as randomized. The critical values at the final analyses for each comparison conducted will be determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O-F boundary, taking into account the errors spent at the interim efficacy analyses for that comparison. Cox proportional hazards models, stratified on age, CD20 status, rituximab use, and whether patients intend to receive HSCT or not, will also be used to assess the treatment effect by adjusting other possible clinical and biological risk factors, including cytogenetic abnormalities.

The rate of HSCT in each treatment arm will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). To assess the potential impact of transplant on the primary comparison, at the time of final analysis, a sensitivity analysis will be performed. A Cox proportional hazards model of OS, stratified on MRD status, age, CD20 status, and rituximab use, will be used to assess the effect of treatment and will include receipt of transplant as a time-varying covariate.

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9.4 Randomization Scheme

Randomized treatment codes will be assigned using a permuted blocks within strata algorithm with dynamic balancing on institution (with main institutions combined with their affiliate networks for balancing). Treatment codes are generated by the ECOG-ACRIN Patient Registration System (PRS) using a computerized random number generator to produce permuted blocks of treatment codes for each stratum. The block size is the blocking factor multiplied by the number of treatments. The number of possible permutations depends on the block size and resulting number of individual treatments. Treatment assignments are consumed sequentially and within each stratum. The stratification factors for this study are: MRD status (positive vs. negative), age (30-54 vs. ≥ 55 years), CD20 status (positive vs. negative), rituximab use (yes vs. no) and whether patients intend to receive HSCT (yes vs. no). Dynamic balancing is used to maintain treatment balance within main institution and their affiliate networks. As with all NCTN studies, the sites enroll patients through the Oncology Patients Enrollment Network (OPEN) web system, which transmits

information to the PRS system. The PRS system then determines the treatment assignment and transmits the assignment back to OPEN.

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9.5 Interim Analyses of Primary Endpoint

This study will be monitored by the ECOG-ACRIN DSMC. Interim analyses will be performed annually. The first efficacy interim analysis and the first futility interim analysis in the MRD- patients will be performed, when at least 24 events, that is approximately 25% of the planned full information, have occurred in the MRD- patients, and will continue until either criteria for early stopping are met or the full information is reached, except that a scheduled interim analysis will not be performed if small increments of information (< 10%) are gained during twelve months in the MRD- patients. To preserve the overall type I error rate, critical values at the interim efficacy analyses will be determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O'Brien-Fleming (O-F) boundary. If at one of the scheduled interim analyses, the upper O-F efficacy boundary has been crossed, the study may be stopped in favor of effectiveness in the MRD- patients by the DSMC. Table 1 gives the boundary at the expected analysis times under the assumptions detailed above.

Table 1: The Interim Efficacy Analyses for the OS Comparison in MRD patients

Time from Study Start (Years)	Information Time	Events Under H_1	Truncated O-F Boundary
3.0	0.25	24	3.29
4.0	0.40	38	3.29
5.0	0.55	52	2.87
6.0	0.71	67	2.46
7.0	0.86	81	2.22
8.4	1.00	94	2.06

This study will be monitored for early stopping for harm and futility for the OS comparisons in the MRD- patients. At the first interim analysis (about 25% information of MRD- patients), we may consider blinatumomab to be harmful in that population if the lower bound of a 95% confidence interval in the hazard ratio (blinatumomab/no blinatumomab) is above 1. Inefficacy monitoring is scheduled to start approximately after 49% of the full information (46 events) become available in the MRD- patients, with repeated analyses annually at DSMC meeting. Linear 20% Inefficacy Boundaries (LIB20) proposed by Freidlin et al.[48] will be used. At each interim analysis, if the estimated hazard ratio is larger than the cut-off value given in the LIB20 boundary, the DSMC may recommend that that blinatumomab is futile in MRD- patients.

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9.6 Secondary Objectives

As one of the secondary objectives, the relapse-free survival (RFS) of blinatumomab in conjunction with chemotherapy will be compared to chemotherapy alone in MRD- patients after induction and intensification chemotherapy. RFS is defined as time from Step 3 randomization to relapse (defined as in Section 6.4) or to death without documentation of relapse. Patients last known to be alive will be censored at the date of last contact.

For MRD- patients, we assume a 30% long-term cure rate of RFS and 11-month median RFS in the non-cured group in the control arm. With 190 MRD- patients, the study will have 80% power to detect 43% reduction in hazard rate in the blinatumomab arm relative to the no blinatumomab arm, using one-sided log rank test at the significance level of 0.025 and assuming 2 years of follow-up, which is equivalent to detecting an improvement in the 3-year RFS rate from 37% to 57%. The number of events needed is 106.

At the final analysis, estimates of RFS, including medians and confidence intervals, will be calculated using the Kaplan-Meier method. Comparison of RFS between treatment arms will be conducted using the one-sided stratified log-rank test with age, CD20 status, rituximab use, and whether patients intend to receive HSCT or not as stratification factors. Stratified on those factors, Cox proportional hazards models, will also be used to assess the treatment effect by adjusting other possible clinical and biological risk factors, including cytogenetic abnormalities and the receipt of transplant (included as a time-varying covariate).

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From this amendment, after achieving CR/CRi and receiving intensification treatment, patients who are MRD+ will be registered to Step 3 and receive blinatumomab directly on Arm C. Combining with those MRD+ patients randomized to Step 3 blinatumomab arm prior to this amendment, we assume a total of 62 MRD+ will receive blinatumomab on study. As a secondary objective, the OS and RFS of those patients who are MRD+ at step 3 randomization/ registration and then convert to MRD- after 2 cycles of blinatumomab will be compared to those patients who are MRD- at randomization and remain MRD-

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after 2 cycles of blinatumomab or consolidation chemotherapy. Assume 50 (80% of 62) of those MRD+ patients will convert to MRD– after two cycles of blinatumomab and 90 patients (95% of 95 randomized to each arm) who are MRD- at randomization will remain MRD- after 2 cycles of blinatumomab (or consolidation chemotherapy). For MRD+ converting to MRD- patients, we assume a 45% long-term cure rate and 14-month median OS in the non-cured group. The study will have 80% power to detect 56% reduction in hazard rate in the MRD- remain as MRD- patients (after blinatumomab/consolidation chemotherapy), using one-sided log rank test at the significance level of 0.025 and assuming 2 years of follow-up, which is equivalent to detecting an improvement in the 3-year OS rate from 54% to 76%. The number of events needed is 49. At the final analysis, landmark analysis will be performed and only patients with MRD data available after 2 cycles of blinatumomab or consolidation chemotherapy will be included. Comparison of OS and RFS between the groups will be conducted using the one-sided log-rank test. Cox proportional hazards models, will also be used to assess the group effect by adjusting age, CD20 status, rituximab use and other possible clinical and biological risk factors, including cytogenetic abnormalities and the receipt of transplant (included as a time-varying covariate).

In this study, we will also examine the effect of rituximab on CD20+ patients. Among those CD20+ patients entering step 3, OS and RFS of those receiving rituximab will be compared to those not receiving rituximab. Cox regression analysis will be used to examine the rituximab effect, adjusted by blinatumomab treatment effect, MRD status, age, cytogenetic abnormalities, and the receipt of transplant (included as a time-varying covariate).

As per NCI CTCAE, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing.

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9.7 Accrual

Based on the accrual rate of E2993 and also considering the participation of other collaborative groups, we originally estimated the accrual rate per year of this study to be roughly 72 patients. The accrual rate as of May, 2018 is about 116 patients per year. With this accrual rate, we anticipate the enrollment of 488 patients with BCR/ABL-negative B cell precursor ALL could be completed around November 2019.

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9.8 Gender and Ethnicity

Based on previous data from ***E2993*** the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	14	21	35
Not Hispanic or Latino	177	276	453
Ethnic Category: Total of all subjects	191	297	488
Racial Category			
American Indian or Alaskan Native	1	2	3
Asian	8	4	12
Black or African American	14	23	37
Native Hawaiian or other Pacific Islander	0	0	0
White	168	268	436
Racial Category: Total of all subjects	191	297	488

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Rev. 7/14, 6/16

9.9 Correlative Studies

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9.9.1 Identification and Characterization of the BCR/ABL1-like Phenotype[49]

The OS (and RFS) of patients with BCR-ABL-like phenotype will be compared to those without BCR-ABL-like phenotype. It is expected that patients with BCR-ABL-like phenotype will have poor outcome. Assume 40% of patients will have BCR-ABL-like phenotype. We assume a 30% long-term cure rate and 11-month median OS in the non-cured group in patients with BCR-ABL-like phenotype. With approximately 275 patients entering Step 3, the study will have 80% power to detect 37% reduction in hazard rate in patients without BCR-

ABL-like phenotype, using one-sided log rank test at the significance level of 0.025 and assuming 2 years of follow-up. The number of events needed is 156.

Rev. 8/17, 12/17

Cox regression analysis will be used to assess whether BCR-ABL-like phenotype is an independent predictor for OS (and RFS), adjusted by treatment effect, MRD status, age, cytogenetic abnormalities, CD20 status, rituximab use, and whether patients intend to receive HSCT or not. The interaction of treatment and BCR-ABL-like phenotype will be tested in the model. If a strong interaction effect is detected, Cox regression analysis will be used to look at the treatment difference separately within each of the BCR-ABL-like phenotype categories (negative/positive) to see if the magnitude and direction of the treatment effect differs by phenotype.

9.10 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Center.

9.11 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. The DSMC reviews comprehensive toxicity reports twice each year. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.

9.11.1 Early Stopping for Excessive Toxicity

Since little is known about the toxicity of blinatumomab in this treatment paradigm, the tolerability of this regimen will be tested in the first 50 patients treated in the blinatumomab arm. All grade 5 events occur during the first 2 cycles of blinatumomab will be evaluated. We will consider blinatumomab tolerable if the grade 5 events is 5% or less, and intolerable if the rate is 20% or higher. If, in the first 50 patients treated in blinatumomab arm, we observe 6 or more patients with grade 5 events, the DSMC will be consulted regarding a recommendation on the termination of the trial. With this design, the probability of concluding the regimen intolerable is 0.04 if the true but unknown rate of grade 5 events is 5%; the probability of concluding

the regimen intolerable is at least 0.95 if the true but unknown rate of grade 5 events is 20%.

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9.11.2 Monitoring for Infection Rate of 72 or 96 Hour Bag Changes in Blinatumomab Administration

The rate of grade 3 or higher relevant infections (defined as sepsis, bacteremia, device or catheter-related infection) will be monitored among patients who received blinatumomab with the infusion bag changed up to 72 or 96 hours. We will consider 72 or 96 hour bag change is acceptable if the infection rate is 5% or less. All grade 3 or higher relevant infections will be evaluated every six months and the infection rate will be tested to determine whether the true rate is 5% using exact one-sided one-sample binomial test, and the results will be presented to DSMC. If at one of scheduled analyses, the one-sided p-value of the test is less than 0.05, the 72 or 96 hour bag change would be considered unacceptable and the DSMC will be consulted regarding whether the bag change frequency should be changed back to 48 hours. The two-sided 90% confidence interval for the infection rate will also be provided. For example, if at one of scheduled analyses, 35 patients were treated in blinatumomab arm with the 72 or 96 hour bag change, with the monitoring rule as described above, the 72 or 96 hour bag change would be considered unacceptable if we observe 5 or more patients with grade 3 or higher relevant infection. At this time point (with 35 patients), the probability of concluding 72 or 96 hour bag change is unacceptable is 0.03 if the true but unknown rate of grade 3 or higher relevant infections is 5%; the probability of concluding 72 or 96 hour bag change is unacceptable is 0.27 if the true but unknown rate of grade 3 or higher relevant infections is 10%; and the probability of concluding 72 or 96 hour bag change is unacceptable is 0.86 if the true but unknown rate of grade 3 or higher relevant infections is 20%. The overall probability of concluding that the 72 or 96 hour bag change is unacceptable depends on the number of analyses and the number of patients treated at the times of those analyses.

Rev. 7/14

10. Research Sample Submissions

NOTE: For institutions outside of the United States, special arrangements have been made between the LTRL and submitting institutions. Laboratories in Israel have been harmonized with the LTRL both for BCR-ABL PCR and flow cytometric assessments of baseline eligibility and MRD levels. Residual material for laboratory research studies will be banked in these laboratories, as instructed by Dr. Elisabeth Paietta, and mailed frozen to the LTRL in batches. Institutions in Canada will send fresh bone marrow and blood samples to the LTRL for eligibility and correlative studies as well as banking.

Rev.6/16

Bone marrow and/or peripheral blood, and karyotypes must be submitted for central diagnostic review. Bone marrow **must be submitted at all other time points** for the mandatory laboratory research studies being performed at the ECOG-ACRIN LTRL. Additional peripheral blood and buccal swabs/rinse are to be submitted from consenting patients for defined laboratory research studies and/or future undefined research studies. These laboratory research studies are defined in Section 11.

Rev. 7/14

The IRB approved consent must allow patients the option to provide specimens for use in the optional defined laboratory research studies and/or for undefined future research studies. Failure to allow this option will result in a major violation at the time of an audit.

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS) (see Section 10.6). An STS shipping manifest form is to be included with every submission.

Rev. 7/14

All samples must be labeled clearly with the ECOG-ACRIN protocol number (E1910), ECOG-ACRIN patient sequence number, patient's initials, date of collection and sample type.

10.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

Rev. 6/16

10.1.1 Bone marrow (first pull), peripheral blood, smears, and buccal swabs/rinse are to be submitted to the ECOG-ACRIN LTRL as outlined in Section 10.2 on the day of collection. Samples are to be collected at the following time points (refer to the table in Section 7.2 for the specific time points and consent levels for each sample type):

- Pre-Registration:

The ECOG-ACRIN Leukemia Translational Research Laboratory will inform institutions of patient eligibility the day of sample receipt, provided they arrive before noon. Samples received after noon will be reported out the following day. Eligibility confirmation includes both the diagnosis of B-lineage ALL and BCR/ABL-negativity.

Samples must be submitted to the ECOG-ACRIN Leukemia Translational Research Laboratory at the following time-points:

Rev. 3/15

- Prior to Start of Treatment
- Post Cycle One (1) of Induction Chemotherapy (day 28)
- Post Cycle Two (2) of Induction Chemotherapy (at time of count recovery)

- Prior to Randomization / Post Intensification

Rev. Add14

- Post Cycle One (1) of Blinatumomab (MRD Positive Pts at Step 3 Registration and HSCT patients only)
- Post Initial Two (2) Cycles of Blinatumomab / Post Cycle Two (2) of Consolidation
- Suspected/Confirmed Relapse

NOTE: FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

Rev. 7/14

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

Rev. 3/15

MRD results are reported when available except for Pre-Randomization which is reported within 7-10 days after sample receipt.

The results for samples from suspected relapse will be provided the day of sample receipt.

Rev. 7/14

10.1.2 Karyotype images are to be submitted via Medidata Rave as outlined in Section 10.3 within one (1) month of collection at the following time points:

- Prior to Start of Treatment
- Post Cycle 1 of Induction Chemotherapy (day 28)*

Rev. 12/15

- Post Cycle 2 of Induction Chemotherapy (at time of count recovery)*
- Relapse
- ***NOTE:** Cytogenetic submission not necessary prior study demonstrated normal karyotype (with at least 20 bone marrow metaphases analyzed). They should be repeated at each time point if abnormal at baseline or less than 20 bone marrow metaphases are analyzed.

10.1.3 Peripheral blood (serum) must be submitted to LabConnect as outlined in Section 10.4 on the day of collection. Samples are to be collected at the following time points from Arm C patients:

Rev. 7/14

Rev. 3/15

- Post Randomization. Prior to Start of Treatment
- Prior to Cycle Three (3) of Treatment

- Prior to Cycle Four (4) of Consolidation with Blinatumomab (Cycle 3 of Blinatumomab)
- Post Consolidation / Prior to Start of Maintenance

Rev. 7/14

10.2 Submissions to ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL)

NOTE: All cooperative groups should send specimens to the ECOG-ACRIN Leukemia Translational Research Laboratory.

Dr. Paietta's institutional regulations require that she receive a copy of the patient's consent and a copy of the HIPAA authorization at the time of or prior to the submission of the baseline samples.

Rev. 7/14

10.2.1 Sample Preparation Guidelines

NOTE: FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

Rev. 6/16

Rev. 7/14

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

Rev. 3/15, 8/17

MRD and CD20 status results will be reported to the submitting institution.

The following are to be submitted:

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1. MANDATORY AT ALL TIME POINTS: Heparinized bone marrow aspirate (the laboratory will accept any amount as long as it represents a first pull)
2. Heparinized or EDTA peripheral blood (four (4) green or purple top tubes, 30-40mL).
   - BASELINE MANDATORY
   - Additional time points from patients who answer "Yes" to "*I agree to participate in the laboratory research studies that are being done as part of this clinical trial.*"
3. Two (2) red top serum tubes of peripheral blood (15-20mL).
   - From patients who answer "Yes" to "*I agree to provide additional specimens for research."*
4. MANDATORY AT ALL TIME POINTS: At least two (2) Wright-Giemsa stained bone marrow smears and one (1) Wright-Giemsa stained peripheral blood smear.

NOTE: These smears will be forwarded to Dr. Daniel Arber at Stanford University for morphologic review, if necessary.

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5. MANDATORY AT ALL TIME POINTS: A copy of the institutional pathology report on the bone marrow must be submitted via Medidata Rave. The pathology report must include cytogenetic results and any results from fluorescence-in-situ (FISH) hybridization and/or molecular studies done at the submitting institution.

   These documents are to be submitted via Medidata Rave

   If Rave is unavailable, please fax to the LTRL at (718) 920-1161

6. Buccal Cell Samples

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- Preferably, Scope, a commercial brand mouthwash, or normal saline in a small sealed bottle can be given to the patient for a mouthwash. Brushes or buccal swabs are acceptable though commonly do not yield sufficient germline DNA.
- Aseptic techniques must be used to collect buccal cells from patients on-site and buccal cells must not be contaminated with cells from any other source. Patients should not brush their teeth or consume food prior to buccal cell collection.
- If a cytobrush is used, the collection end should not be touched and the patient should not scrape his/her cheek too vigorously. The inside of the cheek should be scraped 6 times. Several models of cytobrushes are available, such as the Omni swab or Bio-Swab from Arrowhead Forensics or the Cyto-Pak CytoSoft Brush from Medical Packaging Corp.
- If mouthwash (e.g., Scope) or normal saline is used, the patient should pour approximately 10cc of mouthwash or saline into his/her mouth and vigorously swish it against the cheeks for 10 seconds and deliver the solution into a labeled 50mL sterile polypropylene test tube or a sterile urine cup. Among mouthwashes, the Scope brand fares best in collecting buccal cells for the preparation of high-quality DNA in high yield.
- It is important that buccal cells do not dry out during shipping. Institutions are advised to seal the container containing the buccal cells tightly. Ship containers on ice-packs, together with the patient's peripheral blood and bone marrow specimens.
- Submit from patients who answer "Yes" to "*I agree to provide additional specimens for research."*

  NOTE*:* Buccal rinse (preferred) or swabs are strongly encouraged to be collected prior to the start of treatment, but can be collected at any other time during the study, if necessary.

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10.2.2 Shipping Procedures

The LTRL must be notified by telephone or email the day of shipment for ALL shipments, including follow-up submissions.

The laboratory must be aware that specimens are forthcoming as immediate processing is essential to the integrity of the specimens.

Telephone: (718) 920-4100

During off hours, all information regarding the shipment should be left on the answering machine in the LTRL including:

E1910 sequence number

Patient Initials

Type of specimens shipped

Name, telephone number, and institution

For questions regarding the shipment, Dr. Paietta and her staff can be reached at the phone numbers provided on the recorded message, please always try Dr. Paietta first. Questions can also be addressed to Dr. Paietta via e-mail (epaietta@earthlink.net or epaietta@montefiore.org) or by calling her cell phone (914-806-0345).

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Heparinized bone marrow and peripheral blood or EDTA samples, coagulated blood in red top tubes and buccal cells must be sent fresh (on the day of collection) on **cool packs** (do not freeze and do not use ice cubes) by overnight courier (preferably Federal Express) to arrive within 24 hours to:

Elisabeth Paietta, Ph.D.Department of Oncology
Hofheimer 3rd Floor
Leukemia Oncology Laboratory
111 East 210th Street
Bronx, NY 10467
Tel: (718) 920-4100
FAX: (718) 920-1161
Email: epaietta@earthlink.net

It is imperative that all E1910 specimens be shipped by Fedex FIRST OVERNIGHT DELIVERY (FO), as this will allow the LTRL to run PCR on baseline specimens the day of specimen receipt and will allow for the long acquisitioin of follow-up specimens.

The LTRL is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have “Saturday Delivery” marked on the overnight courier slip. Also, please label the package with a hand-written note that says: “Deliver to Hospital Main Lobby/Security”.

In general, always ship specimens the day before a holiday for delivery the day after the holiday.

An STS shipping manifest form must be generated and shipped with all sample submissions.

Please enter all information into the STS, including time and date of specimen collection and peripheral blood WBC count and blast count.

If samples need to be drawn late at night, on Sunday, or on a holiday when Federal Express does not operate, keep the samples in a refrigerator between 10 and 15 degrees Celsius until the next day when it can be shipped.

10.3 Submissions to ECOG-ACRIN Cytogenetic Laboratory

Direct questions to Gary Hicks at Tel: (507) 284-2950 or Fax: (507) 284-0043.

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10.3.1 Sample Preparation Guidelines

Karyotypes (MANDATORY AT ALL TIME POINTS)

Within 30 days of specimen collection at each time point, investigators must submit two (2) original karyotypes per clone, FISH results, institution's cytogenetic laboratory report, and the Leukemia Cytogenetic Form (#365R) via Medidata Rave.

NOTE: If cytogenetic studies are not successful, submit the laboratory report and #365R form

NOTE: Karyotypes are not to be logged and tracked via the ECOG-ACRIN Sample Tracking System.

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10.4 Submissions to LabConnect

Peripheral blood for serum must be submitted at all time points outlined in Section 10.1.3 to LabConnect. Collection and shipping kits are available. To obtain starter kits please enter the kit shipping address in OPEN during step 2 registration. Initial kit orders take about one-two weeks for delivery.

If you have any questions, please contact LabConnect Investigator Support Services at (800) 501-7947.

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Please refer to the Laboratory Manual provided in the initial kit for details on Specimen Collection and Shipment Preparation Guidelines. If you require the Laboratory Manual for IRB review please contact Chelsea Van Bastelaar (805-630-0357 or cvanbastelaar@labconnectllc.com). Please use the resupply order form found in the lab manual for future kit orders.

LabConnect will forward blood samples to Amgen quarterly for analysis.

An STS shipping manifest form must be generated and shipped with all sample submissions

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10.5 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

10.5.1 Study Specific Notes

Generic Specimen Submission Form (#2981v2) will be required only if STS is unavailable at time of sample submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory. Indicate the appropriate Lab ID# on the submission form:

- 0002 = ECOG-ACRIN Leukemia Translational Research Laboratory
- 0174 = LabConnect

Retroactively, enter all specimen collection and shipping information when STS is available.

NOTE: LabConnect will not be utilizing the STS to confirm receipt.

10.6 Use of Specimens in Research

Specimens will be distributed to investigators for the defined laboratory research studies outlined in Section 11.

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies will be retained in the ECOG-ACRIN Leukemia Tissue Bank (LTB).

Specimens submitted will be processed to maximize their utility for current and future research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study.

10.7 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded by the LTRL/LTB and utilized for approved laboratory research studies will be submitted by the LTRL/LTB to the ECOG-ACRIN Operations Office – Boston on a monthly basis in an electronic format.

10.8 Banking

The residuals and/or derivatives of the samples collected for this study will be retained at the LTRL/LTB for possible use in ECOG-ACRIN approved future

research studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11. Leukemia Correlative Studies

11.1 Immunophenotype and Molecular Genetics

Immunophenotyping has become an essential part of the diagnostic work-up of all leukemia patients. In fact, the diagnosis of leukemia without immunophenotypic characterization is no longer acceptable. ECOG-ACRIN has, therefore, developed a model system for antigenic data collection that requests specimens from all patients entered on ECOG-ACRIN leukemia treatment trials be studied by the ECOG-ACRIN LTRL. In addition to establishing the leukemia subtype, this centralized testing and data collection has allowed that research questions of clinical relevance to be applied to a growing database (e.g., definition of prognostically significant antigen expression levels to eventually yield specific treatment subcategories). Depending on the study protocol and tissue availability, anti-coagulated (heparin, EDTA, ACD) peripheral blood or bone marrow or both are to be submitted to the LTRL. In E1910, an additional significance for central immunophenotyping is provided by the flow cytometric assessment of minimal residual disease (MRD). Sample submissions for MRD determination in bone marrow aspirates will coincide with clinically required bone marrow examinations.

In addition to the study of abnormal hematopoietic cells, the focus of research on circulating serum factors in patients with leukemia or myelodysplasia has increased. Two tubes of coagulated peripheral blood (red top tubes) are requested for future research studies that may aim at identifying pathogenetic, diagnostic, or prognostic factors associated with leukemia or myelodysplasia.

Serum and cells from peripheral blood or bone marrow from patients entered on studies of hematologic malignancies are stored in ECOG-ACRIN's LTB for E1910 embedded and future laboratory studies. The bank provides the scientific community with a source of leukemia specimens that are collected, processed, and maintained following quality control and quality assurance guidelines. The bank will accommodate requests from investigators within and outside ECOG-ACRIN in a timely and efficient manner, with respect to tissue type, tissue preparation, and most importantly, biologic characteristics of specimens.

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11.2 Sample Collection and Banking

Establishment of Immunophenotype and BCR/ABL Status to Determine Eligibility, Minimal Residual Disease (MRD) Monitoring, - Integrated Genomic, Epigenomic, and Metabolic Profiling.

11.2.1 ECOG-ACRIN’s Centralized Collection, Characterization and Distribution of Leukemia Specimens:

Specimens from ECOG-ACRIN and non-ECOG-ACRIN patients MUST be submitted to the ECOG-ACRIN LTRL at all time-points of the study. All patients will be required to submit bone marrow and peripheral blood specimens to the LTRL for eligibility testing. The ECOG-ACRIN LTRL will assess the BCR/ABL status of patients, perform central flow cytometric cytometry for eligibility testing and MRD testing as well as banking for all E1910 patients. The LTRL will

also prepare and distribute viably frozen mononuclear cells from baseline samples for the studies on BCR-ABL-like phenotype.

Our track record indicates that the LTRL receives diagnostic specimens on at least 95% of phase III patients and is successful in obtaining an informative immunophenotype on about 99% of these patients. Initial flow cytometric evaluation will characterize B- lineage ALL based on established criteria,[50, 51] as well as establish the BCR/ABL status by multiplex qualitative (PCR).[52] The initial antibody panel will contain at a minimum all antibodies planned for MRD testing. Antibodies suitable for monitoring of MRD a) distinguish leukemic blasts from normal B-cell precursors (hematogones) in bone marrow; b) detect expression of lineage-foreign markers, e.g., myeloid antigens (e.g., CD33, CD65), c) detect altered density of B-lineage and lineage-uncommitted antigens, (e.g., CD20, CD58) or d) detect asynchronous expression of antigens, (e.g., CD44. CD123).

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Given the novelty of blinatumomab, potential changes in the leukemia-specific signatures due to treatment cannot be predicted, e.g., similar to those seen with glucocorticoids.[53] However, relapses with $CD19^{NEG}$ B-lymphoblasts have been reported following blinatumomab.[42]

Specimens will be sent by overnight mail to the LTRL which also houses LTB, which are both managed by Dr. Elisabeth Paietta at Montefiore Medical Center-North Division in Bronx, NY. Results of testing diagnostic specimens and patient eligibility will be reported to referring institutions within 4-6 hours of sample receipt. PCR for BCR/ABL will be performed within 24 hours of sample receipt. Bone marrow smears will be stored for potential morphology review, if deemed necessary. Bone marrow smears can also serve as a source for DNA if no other material can be banked. Preparation of RNA and DNA will be a priority after establishing the basic diagnosis for the performance of PCR for other leukemia-specific transcripts, including TEL/AML1, E2A/PBX1, and MLL/AF4, mutation analyses, and epigenetic studies. Viable cells will be frozen to allow investigators to sort leukemic lymphoblasts and normal cells, if required. Central immunophenotyping and molecular studies, as done by ECOG-ACRIN, are a vital advantage in a study like this, since they allow for the use of identical antibody panels and interpretation by a single investigator (E. Paietta) for all patients both at the time of presentation and during MRD monitoring (see below for MRD standardization). Residual cells will be banked for embedded and for future research.

The only ECOG-ACRIN institutions exempted from the submission of fresh material for eligibility studies will be Rambam Medical Center in Haifa, Israel and Shaare Zedek Hospital in Jerusalem, Israel. Based on our current experience on E2906, flow cytometric studies and BCR/ABL evaluation by PCR will be done by laboratories in Jerusalem and flow cytometric files and BCR/ABL reports will be sent to the ECOG-ACRIN LTRL via e-mail. Dr. Paietta has communicated with the flow cytometry laboratory at Shaare Zedek and ensured that the standard MRD panel is set up. Flow cytometry files of MRD data

will be sent electronically to Dr. Paietta for immediate MRD evaluation at the time of patient randomization. Other MRD time-points will be assessed by the LTRL retrospectively based on submitted flow cytometry files. Initial testing for BCR/ABL on Israel patients will be done by Dr. Dvora Sahar, in the Hematology Laboratory of the Rambam Hhealth Care Campus in Haifa. Dr. Paietta has harmonized the BCR/ABCL PCR assay done in the LTRL with that performed by Dr. Sahar.

Institutions will submit anti-coagulated bone marrow and peripheral blood as well as 2 tubes with coagulated blood (for serum) to the LTRL. The laboratory will perform eligibility testing on bone marrow preferentially, while peripheral blood mononuclear cells (MNC) are banked, if targeted flow cytometry (to establish the blast count only) has demonstrated the presence of circulating lymphoblasts. Plasma will be separated and frozen for future studies from the anti-coagulated blood, while serum will be separated and frozen for future studies from coagulated blood, as routinely performed on ECOG-ACRIN leukemia trials. Buccal cells are requested at baseline or at any of the follow-up time-points (if patients' mucositis or other logistics prevent collection of buccal cells at study entry) for isolation of germline DNA and banked at the LTB.

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At all MRD time-points, aliquots of unseparated heparinized bone marrow aspirate and peripheral blood, containing between $2x10^6$ and $10x10^6$ white blood cells (dependent on availability), will be subjected to red cell lysis (e.g., with ammonium chloride Lysing Buffer). Cell pellets will be resuspended in Gentra Lysis buffer (Qiagen) and banked at 4˚C for future DNA isolation, as done routinely in the LTRL for molecular MRD determination. During the course of this protocol, DNA will be isolated from these lysates by the LTRL and DNA will be stored at -80ºC until distribution (stable indefinitely). These specimens, which will serve the development of a companion diagnostic, will be retained for Amgen and/or their designated third party vendor until such time it is clear that a companion diagnostic is needed and the specific platform for molecular MRD assessment and vendor are identified. Once this determination is made, Amgen will notify ECOG-ACRIN and CTEP of specific plans (along with any FDA regulatory information to assure the companion diagnostic will be accepted by the Agency). This information will be reviewed in order to release the specimens for the appropriate companion diagnostic. ECOG-ACRIN will retain a minimum DNA quantity on every patient with adequate specimen collection for future correlative studies, provided that the request by Amgen or their designated third party vendor has been satisfied. The specimens for Amgen will not otherwise be released unless it is determined that a companion diagnostic is not needed for drug labeling.

For molecular studies, other than molecular MRD assessment, DNA (from 2-5 million cells) and RNA (usually from 5-10 million cells) will be isolated from mononuclear cells (MNC), obtained by density gradient centrifugation, to ensure blast enrichment. MNC cells that are

left over after preparation of cell lysates for nucleic acid isolation will be banked in 90% fetal bovine serum and 10% dimethylsulfoxide (DMSO) at 20-50 million cells per 1.8ml aliquot. Cells frozen under these conditions at ultralow temperature (-120ºC) remain viable after thawing even when stored for 10-20 years (experience by LTB). At the time of presentation, the percentage of lymphoblasts in the MNC fraction – compared to that in whole, unseparated tissues – will be established by flow cytometry and provided to the investigators who request banked specimens.

Mononuclear cells from baseline marrow or blood will be frozen in a viable state and aliquots of 20-40 million MNC will be shipped to Drs. C. Mullighan/C. Willman for the assessment of the BCR-ABL-like phenotype. Any left-over material will be banked for future research, provided that patients have consented to that in the E1910 consent. To be absolutely certain that a patient's wishes are respected, ECOG-ACRIN's LTRL routinely collects and keeps on file a paper copy of the patient's consent to the use and storage of biologic material. Since the laboratory collects personal information, it also keeps a copy of the patient's HIPAA Authorization form. Any material that is received by ECOG-ACRIN's LTRL is immediately stripped of personal identifiers and coded by a unique laboratory identifier, a specimen accession number. Bone marrow and peripheral blood samples from one patient taken at the same time-point (e.g., at diagnosis), even if received on different dates (e.g., BM on 10/3/09 and PB on 10/4/09 but both are from diagnosis, prior to initiation of therapy) receive the identical accession number. Multiple specimen submissions from the same patient on different dates are coded with distinct accession numbers, while the E1910 sequence numbers link all submissions to the same patient. Vials containing frozen cells serum/plasma, or nucleic acids are labeled with the accession number, the specimen date, and the specimen type but NOT the parent protocol sequence number; therefore, any investigator receiving those materials will be unable to link the cells received to a particular patient.

Specimens from E1910 patients from participating, non-ECOG-ACRIN groups will likewise be received by the ECOG-ACRIN LTRL and treated the same way as ECOG-ACRIN patients. Any patient considered a candidate for E1910 will sign the E1910 consent, including consent for central laboratory testing, prior to specimens being sent to the ECOG-ACRIN LTRL.

The results from cytogenetic analysis, FISH and any molecular tests performed at the submitting institutions will also be submitted to ECOG-ACRIN's LTRL, as part of the pathology report. Dr. Paietta will enter those results in her comprehensive leukemia database. ECOG-ACRIN institutions submit bone marrow (or rarely peripheral blood) for cytogenetic studies to the cytogenetic laboratory preferred by each institution. Results from that analysis plus two representative karyotypes are subsequently submitted to the ECOG-ACRIN Cytogenetics Committee for review. Once accepted, the chair of the ECOG-ACRIN Cytogenetics Committee, Yanming Zhang at

Northwestern University, Chicago, IL, or his representative, Gary Hicks at Mayo, Rochester, MN, will mail those results via secured electronic submission to the ECOG-ACRIN Operations Office – Boston and to Dr. Paietta, who will enter those results in her comprehensive leukemia database.

11.2.2 Monitoring of Minimal Residual Disease (MRD)

11.2.2.1 Hypotheses:

a) MRD levels at various time-points and particularly before and after blinatumomab therapy are associated with outcome

b) Blinatumomab therapy successfully eradicates MRD.

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11.2.2.2 Correlative Study Design

There is solid evidence indicating that MRD testing is clinically useful in pediatric and adult ALL[54,55], including the recent ECOG phase III trial, E2993[22]. Comparative studies of MRD assessment by PCR and flow cytometry have proven the two methodologies to be equally reliable in terms of sensitivity, specificity, and reproducibility [54, 56-58]. However, flow cytometry delivers results much more rapidly and at considerably lower costs. Therefore, in E1910, MRD levels will be assessed by flow cytometry as integrated markers 4 times during the trial and as an integral marker prior to randomization. MRD positive patients will be assigned to blinatumomab while MRD negative patients will be randomized between blinatumomab and consolidation chemotherapy. Patients will not be randomized until they have completed intensification and the E1910 ECOG-ACRIN statistician has been informed of the bone marrow MRD result by the LTRL.

All NCTN flow cytometry reference laboratories are currently involved in an NCI-led standardization effort for flow cytometric MRD evaluation in ALL. We will utilize antibody combinations selected by the NCI-led MRD standardization group (ECOG-ACRIN, SWOG and CALGB/ALLIANCE). Auxiliary antibodies can be added if needed. The first 2 tubes are modeled after the MRD panel developed and used by the Children's Oncology Group (COG), given the unrivaled experience of COG in ALL MRD.

The 3rd tube includes CD22 as well as the myeloid antibodies [CD15 and CD65] which are frequently expressed by leukemic blasts with KMT2A gene rearrangement.

The 4th tube measures the fraction of nucleated cells that are B cells with the Syto16 dye. Eventually, MRD is

expressed as a fraction of all nucleated cells, as routinely done in the LTRL. CD71 in the 4th tube detects nucleated erythroid cells which are excluded from the calculation.

1. Standardized MRD Antibody Panel

TUBE	FLUOROCHROMES (Excitation-Max/Emission-Max in nm)					
	FITC (494/520)	PE (496/578)	PC5.5/ PerCPCy5.5 (488/692)	PECy7 496/785)	APC (650/660)	APC-H7 (650/785)
1	CD20	CD10	CD38	CD19	CD58	CD45
2	CD9	CD13+CD33	CD34	CD19	CD10	CD45
3	CD65+CD15	CD58	CD22	CD19	CD10	CD45
4	Syto16		CD3	CD19	CD71	CD45

FITC, fluorescein isothiocyanate; PE, R-phycoerythrin; PC5.5, R-phycoerythrin-cyanine 5.5; PerCP Cy5.5, Peridinin–chlorophyll cyanine 5.5; PC7, phycoerythrin-cyanine 7; APC, allophycocyanin; APC-H7, allophycocyanin-cyanine tandem dye.7

The above panel is still a work in progress and may change as the result of upcoming NCI-meetings.

Given the impact of MRD levels on randomization and trial analysis, flow cytometric MRD assessment will have highest priority for sample usage. While at presentation, small sample aliquots are usually sufficient to establish the diagnosis, given the elevated blast count, larger sample amounts will be required following treatment.

At baseline, WBC counts will be adjusted to 10^7 WBC/ml. If the cell count is at least 3 times higher than that, samples will be diluted with HEPES-buffer containing human AB and fetal bovine serum (IFA buffer) to the desired concentration; for slightly higher cell counts, sample volume can be reduced from 20µl per antibody tube for a $1x10^7$/ml cell suspension to a proportionate volume. For baseline samples with low WBC counts, a larger sample volume up to 200µl per antibody combination can be used. At MRD time-points, cell counts can be extremely low, making it necessary to concentrate samples using an ammonium chloride red cell lysing buffer, as recommended by the NCI MRD Working Group. It is important that sufficient white cells be stained with antibodies to allow > 500,000 (optimally 1 million) cells to be acquired for adequate sensitivity. Staining with antibodies will be done for 30 minutes at RT in the dark; excessive antibody will be washed away with IFA buffer before red cell lysis (unless red cell lysis was done prior to staining) and cell fixation with formaldehyde- containing red cell lysis buffer. Prior to

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acquisition, fixed cells will be washed and resuspended in PBS. An aliquot of cells will be incubated with the Syto16 dye for 10 minutes at RT in the dark prior to acquisition. Stained cells will be acquired on a FACSCanto II (Beckton-Dickinson, BD) flow cytometer.

All MRD results in E1910 will be derived from bone marrow aspirates based on data showing that in pediatric B-lineage ALL MRD levels are much lower in peripheral blood than bone marrow both by molecular[60] and flow cytometric evaluation[61]. ECOG-ACRIN has seen identical results in adult trials E2993 with PCR and in C10403 with flow cytometric MRD determination (Paietta E, unpublished).

The ECOG-ACRIN LTRL will perform all MRD testing. All samples will be sent to this laboratory for initial characterization and subsequently for MRD testing. The randomization stratification will be based on the LTRL result, following the NCI's suggestion to assess the integral marker only in one laboratory. This routing of specimens is preferred over the use of individual group laboratories for non-ECOG-ACRIN specimens to ensure optimal sample collection and does not reflect reservations regarding the standards of MRD testing in non-ECOG-ACRIN flow cytometry cores. The LTRL has ample experience in assessing immunologic MRD in both AML (E1900, E2906) and ALL trials (E2993, C10403, S0805). Concerns regarding standardization of flow cytometric MRD assays among group laboratories have largely diminished with the NCI-led standardization effort which demonstrated that the LTRL produced data comparable to those provided by the COG laboratories, the laboratories with more experience in flow cytometric MRD analysis than any other laboratory in the country. Adult leukemia trials present with their own specific challenges, in particular, the timely sample collection for MRD assessment and the quality of samples for MRD testing. For instance, in pediatric trials, the submission of a separate or first bone marrow aspirate for MRD studies has become routine, while in adult trials, the aspirates submitted are largely contaminated with peripheral blood, indicating that the second or even third pull was submitted. The LTRL has, therefore, engaged in close interactions with participating institutions to emphasize the need for sample quality. Over the last few years, as a result of these efforts, the submission of follow-up specimens has markedly improved-however, to optimize sample collection on E1910, ECOG-ACRIN will utilize automated email reminders to be incorporated into the new Rave clinical management system. Given that all groups will log into the ECOG-ACRIN instance of Rave,

this system will allow us to monitor all E1910 patients, irrespective of group affiliation.

Regarding the quality of bone marrow aspirates, the technique of bone marrow aspiration has been shown to impact the MRD level measured in the aspirate[62]. In particular, the common procedure to aspirate a small sample of marrow (2ml) for morphologic examination and thereafter, without changing the position of the needle, to aspirate 5-10cc of marrow for flow cytometry results in an underestimation of MRD levels. Therefore, the amount of MRD should be measured by flow cytometry (or molecular techniques) in the first 2.5cc of bone marrow aspirated from one puncture site. In fact, MRD-guided COG protocols include such directive (Brent Wood, personal communication). Dr. Paietta will continue to hold repeated presentations in the general Education Session for Clinical Trial Professionals during the semiannual ECOG-ACRIN meetings (the first one occurred in November, 2012), to convey this information to CRAs, nurses and fellows. In addition, a memorandum will be distributed by ECOG-ACRIN to all participating institutions carrying the same message. Drs Paietta and Litzow will communicate with the Leukemia Committee chairs from other cooperative groups to ensure proper bone marrow sampling.

Although MRD is quantified as a continuous variable, reflected by the percentage of blasts among all nucleated cells, the data will be used for randomization qualitatively, non-ordered categorical (MRD+ versus MRD-). The value that will be used to dichotomize into MRD+ and MRD- will be 10^{-4} or 0.01% of leukemic cells among all normal nucleated cells. In each antibody tube, MRD, if present, will be detected independently by setting a series of sequential gates that exclude normal cells at each step, until a distinct population of abnormal cells remains.

This commonly used cut-off level for the definition of flow cytometric MRD positivity,1 target cell in 10^4 normal cells, is a realistic sensitivity for clinical samples and found to be predictive of outcome in pediatric and adult ALL. The backbone of the common MRD antibody panel in E1910 consists of CD45, CD19, and CD10 to detect B-cell precursors (leukemic and normal). The first gate identifies lymphocytes by CD45 versus cellular granularity (side scatter). CD45 is typically expressed by leukemic blasts at a density lower than that of normal lymphocytes. Next, $CD19^{POS}$ cells are spotted in the $CD45^{LOW}$ population, followed by detection of CD10 in the $CD45^{LOW}CD19^{POS}$ gate. In the $CD45^{LOW}CD19^{POS}CD10^{POS}$ or $CD10^{NEG}$ gate (if initial blasts were $CD10^{NEG}$) We will use the COG Different-from-Normal approach to distinguish residual leukemic B-

lymphoblasts from hematogones (normal B-lymphoid bone marrow precursors). The incidence of hematogones decreases as a function of age, but is particularly elevated after chemotherapy. Leukemic antigen features must be identified on a certain number of cells ('cluster'). Dependent on the number of cells in the abnormal cluster and the total number of normal cells present, abnormal cells can be recognized at a level of sensitivity of ≤ 10^{-4}. Because leukemic cells are directly quantified in relation to other cells in the specimen, there is no need for external calibrators. In the ECOG-ACRIN LTRL, clusters that are considered to represent MRD may constitute as few as 15-20 cells (sensitivity reaching < 10^{-4}). The analysis software used on the FACSCanto II flow cytometer is FACS DIVA version 6.

11.3 Identification and Characterization of Patients with BCR/ABL1-like Phenotype

11.3.1 Hypotheses:

11.3.1.1 The incidence of the BCR/ABL1-like phenotype is considerably higher in older adults than in children or adolescents with B-lineage ALL.

11.3.1.2 As previously seen in children, the outcome of patients with BCR/ABL1-like phenotype is also poor in adults, independent of MRD.

11.3.1.3 As in children, the BCR/ABL1-like phenotype in adults is associated with a spectrum of tyrosine kinase mutations/translocations resulting in tyrosine kinase activation.

11.3.1.4 Blinatumomab can efficiently eradicate MRD also in B-lineage ALL with the BCR/ABL1-like phenotype.

ALL remains an important cause of morbidity and mortality in adults, with event-free and OS substantially inferior to those observed in children. The biologic basis of this poor outcome is incompletely understood. Recent genome wide profiling studies identified recurrent alterations in pediatric ALL, including alterations in early B lineage transcription factor genes (*PAX5, IKZF1, EBF1*). Deletion or, less commonly, alteration of *IKZF1* (encoding the early lymphoid transcription factor IKAROS), is associated with risk of treatment failure, and is a hallmark of two subtypes of leukemia: BCR-ABL1^{POS} ALL and BCR/ABL1-like phenotype ALL.[49,63,64]

BCR/ABL1-like ALL comprises 15% of childhood B-progenitor ALL[65-69]. These cases exhibit a gene expression profile similar to that of BCR-ABL1^{POS} ALL, harbor *IKZF1* alterations, and respond poorly to contemporary ALL therapy. Up to 50% of these cases harbor a rearrangement of *CRLF2* (cytokine receptor like factor 2), either as an

IGH@-CRLF2 rearrangement, or a focal deletion proximal of *CRLF2,* that results in expression of the *P2RY8-CRLF2* fusion. Less commonly, a *CRLF2* F232C mutation is present. Half of *CRLF2* rearranged cases harbor concomitant activating JAK mutations, and all *CRLF2* rearranged cases exhibit constitutively active JAK-STAT signaling that is attenuated by JAK inhibitors. ALL cells harboring *CRLF2/JAK* alterations are inhibited by JAK inhibitor monotherapy *in vivo.* Exome and RNA-sequencing of childhood BCR/ABL1-like B-ALL cases identified additional kinase activating lesions in the majority of non-CRLF2 rearranged cases. These include chimeric fusions, focal deletions and sequence mutations which activate kinases and signaling effectors including *JAK2, ABL1, PDGFRB, CSF1R, EPOR*, the interleukin 7 receptor gene *IL7R*, and the JAK2 negative regulator *SH2B3* (LNK). Despite the diversity of alterations, these lesions largely converge on a limited number of kinase signaling pathways, most notably ABL1, PDGFRB, and JAK2. Of note, these alterations comprise approximately 80% of Ph-like ALL (unpublished data).

In contrast to pediatric ALL, the genetic basis of adult ALL is poorly understood. Although BCR-ABL1^{POS} and *MLL*-rearranged ALLs are more common in adults, these fail to explain the poor outcome of adult ALL. We have performed genetic studies in about 800 pre-treatment leukemia samples from adolescent and young adults (17-39 years) with ALL (AYA), including 100 patients from ECOG-ACRIN and samples from St. Jude, COG, CALGB/ALLIANCE and MD Anderson Cancer Center. The frequency of BCR/ABL1-like ALL increased with patient age, rising from 25% in adolescents to 35% in young adults. Notably, in the cohort of ECOG-ACRIN cases, BCR/ABL1-like ALL occurred in 23.6%, a frequency approaching that of BCR/ABL1^{POS} ALL (28.9%). Consistent with our previous data, 89% of ECOG-ACRIN BCR/ABL1-like cases had *IKZF1* alterations by SNP array profiling, and all had alterations of genes regulating lymphoid development (e.g., *PAX5 or EBF1*).

Importantly, our studies have shown that many of these alterations are sensitive to TKI therapy. Cell lines expressing ABL1/PDGFRB fusions found in BCR/ABL1-like ALL are sensitive to ABL1/PDGFRB inhibitors including imatinib and dasatinib. Primary patient cells harboring JAK kinase or IL7R/SH2B3 alterations are sensitive to JAK2 inhibitors. Moreover, we have recently seen a childhood case of primary refractory ALL with an underlying cryptic EBF1-PDGFRB translocation which achieved a CR upon addition of imatinib to conventional multi-agent remission induction therapy. Together, these

data indicate that identification of BCR-ABL1-like ALL is warranted to identify those patients who may benefit from TKI therapy or novel therapeutic interventions.

11.3.2 Correlative Study Design:

Sample Distribution and Workflow. As part of the flow cytometric evaluation of baseline specimens, the LTRL will determine the expression of CRLF2 on the surface of leukemic lymphoblasts and report the result to the Willman/Mullighan laboratories. Subsequently. the LTRL will prepare one aliquot of bone marrow or peripheral blood mononuclear cells (with known lymphoblast count) frozen in a viable state in the presence of 90% fetal bovine serum and 10% DMSO for each registered E1910 patient with sufficient cell material. An aliquot of 20-40 million frozen bone marrow or blood MNC will be shipped to Dr. Charles Mullighan, whose laboratory will isolate nucleic acids for RT-PCR analyses and forward the required material (RNA or cDNA) for TLDA analysis to Dr. Cheryl Willman. BCR-ABL-like patients that were found to be CRLF2 negative will be subjected to fusion detection, which is currently done by RT-PCR, though this might be switched to Next Generation Sequencing (NGS) in the lifetime of this protocol. NGS will be performed on all specimens that are negative for known BCR-ABL-like kinase alterations in the Mullighan laboratory. While a minimum of 20 million cells is required, for samples with <70% leukemic cells, fluorescence-activated cell sorting will be performed by the Mullighan laboratory to purify blast populations, thus requiring a higher starting cell count of 40 million cells. Baseline samples will be sent to the Mullighan laboratory batchwise; samples from 10 patients in each batch. If available, left-over DNA will be provided by Dr. Mullighan to Dr. Ross Levine (MSKCC, New York) for the assessment of the JAK mutation status. Alternatively, the required amount of DNA will be prepared by the ECOG-ACRIN LTRL and sent to the Levine laboratory. The intent is to subject all E1910 patients to these analyses, irrespective of chromosomal alterations. Aside from baseline specimens, no further specimens will be needed for these primary analyses. However, genomic DNA from remission samples or buccal cells will be required for subsequent genomic assays distinguishing somatic from inherited variants. Genomic control DNA will be provided by the LTRL.

Targeted Low Density Array (TLDA) Analysis. The gene expression profile of BCR-ABL1-like ALL cases is highly similar to those ALL cases with a BCR-ABL translocation. We will use microarray gene expression profiling to identify cases with BCR-ABL1-like ALL. We have used statistic approaches to identify 12-15 genes that robustly identify BCR-ABL1-like ALL using TLDA cards *(IGJ, SPATS2L, MUC4, CRLF2, CA6, NRXN3, BMPR1B, GPR110, SEMA6A, PON2, CHN2, S100Z, SLCA5, TP53INP1, IFITM1*. We will perform analysis of E1910 cases using TLDA cards to identify BCR-ABL1-like cases.

Flow Cytometric Phosphoflow Analysis. It is the plan to screen BCR-ABL1-like samples based on TLDA analysis for activation of specific kinases by phospho-flow analysis of cryopreserved leukemic cells.

Since this part of the BCR-ABL-like phenotype analysis would require an additional aliquot of cells to be obtained from the ECOG-ACRIN LTB, a separate proposal for phosphoflow analysis will be submitted at a later time-point.

Expected Outcomes: We will use the complementary genomic and proteomic approaches to identify and validate the frequency of BCR-ABL1-like ALL in adult ALL.

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CRLF2 Rearrangement Testing. We will screen for *CRLF2* alterations by flow cytometry of leukemic cells (ECOG-ACRIN – E. Paietta), RT-PCR for P2RY8-CRLF2 (St. Jude – C. Mullighan) and *CRLF2* FISH (UNM – C. Willman). The ECOG-ACRIN LTRL at MSKCC, NY (R. Levine) will perform JAK mutational testing.

RT-PCR for Candidate Fusions. Our current studies in childhood ALL have identified 11 fusions in BCR-ABL1 like ALL. We will perform RT-PCR for these fusions in E1910 BCR-ABL1-like ALL cases.

Next Generation Sequencing Analysis to Identify Novel Alterations. We will subject E1910 cases lacking known alterations to mRNA-sequencing and exome sequencing. Our studies in progress indicate we can identify pathogenic, therapeutically tractable fusions in approximately two thirds of cases. In the remainder, exome sequencing, SNP array analysis and/or whole genome sequencing will be required to identify causative lesions.

Expected Results: We will determine the incidence of BCR-ABL1-like genotype in adults, and the spectrum and nature of the underlying mutations in tyrosine kinases signaling pathways in adult ALL. We will also assess whether Blinatumomab has efficacy in eradicating MRD in BCR-ABL1-like ALL.

This analysis will be performed by Dr. Charles Mullighan at St. Jude Children's Research Hospital and Dr. Cheryl Willman at the University of New Mexico Cancer Research Center.

11.4 Determination of CD20 Expression by leukemic B-lymphoblasts at the time of study entry

CD20 expression is routinely determined by flow cytometry, using a FITC-conjugated antibody, as part of the eligibility testing for E1910 patients. We have noticed 3 distinct patterns of CD20 expression in B-lineage ALL, 1) blasts are completely negative for CD20, 2) blasts are predominantly positive for CD20, and 3) a small fraction of lymphoblasts expresses CD20, consistently between 20 and 30% of the entire leukemia population. This CD20+ subpopulation is not an artifact, it is seen when leukemic blasts are thawed, when different CD20 antibody lot numbers are tested and even with the use of different fluorochromes conjugated to the CD20 antibody.

Rather than using an a priori set cut-off point of antigen expression to call a patient's leukemia population positive or negative, we will recommend rituximab treatment for any patient whose blast cell population shows a distinct population of CD20 staining cells, irrespective of the percentage of CD20+ blasts. The

CD20 result will be entered on RAVE at the time the baseline report will be sent to the referring institution.

11.5 Blinatumomab Immunogenicity Assessment

Blinatumomab is a novel protein therapeutic under clinical development. As outlined in the Draft Guidance: Immunogenicity Assessment for Therapeutic Protein Products (Feb 2013) pre-specified immunogenicity sampling will be performed to evaluate and mitigate risk (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf).

Blood samples for the assessment of blinatumomab immunogenicity will be collected to determine whether anti-idiotype antibodies directed against blinatumomab have been developed. Screening for these antibodies will be done by ELISA assay on ECL Basis (electrochemiluminescence), and binding will be confirmed with a Biacore assay to measure protein-protein interaction and binding affinity.

In a tiered approach patient samples are initially tested in a screening assay. Samples that produce signals above a certain screening cut point (classified as "positive") may be subjected to a confirmatory assay. The screening assay is designed to minimize false negatives, so positive screening assays need to be confirmed as positive. These are performed using the same format as the screening assay. A comparison of patient serum in the presence and absence of excess blinatumomab is used to confirm or deny the existence of anti blinatumomab antibodies. The screening and confirmation assay in the context of blinatumomab clinical studies will be performed according to an internal standardized protocol using a validated assay.

Immunoassay-positive samples will be analyzed in a third step using a cell based blinatumomab-mediated cytotoxicity assay to determine if the detected antibodies have neutralizing properties. Detection of neutralizing anti-blinatumomab antibodies relies on a validated bioassay measuring changes in the biologic activity of blinatumomab triggered by the presence of the antibody.

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Serum samples for antibody testing are being collected on all patients randomized to receiving blinatumomab for the measurement screening of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. The 'cell-based assay' for neutralizing antibody detection tests patient sera in a model cell based system. This does not require patient cells or additional serum to be collected. Both the screening and the neutralizing assays are well-established at the Amgen Research Munich laboratory.

ECOG-ACRIN will be notified of any positive neutralizing antibody results to blinatumomab. If results are not provided, no neutralizing antibodies to blinatumomab have been detected.

Patients who test positive for neutralizing antibodies to blinatumomab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every three months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least one

year (± 4 weeks) post administration of blinatumomab. All follow-up results, both positive and negative will be communicated to ECOG-ACRIN. More frequent testing (e.g. every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab. Patients who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.

11.6 Future Research Studies

The following correlative studies are proposed as outlined below. Final analysis of the proposed studies requires the results of the parent study. When sufficient information is available from the parent study a full correlative science proposal or amended protocol document detailing the scientific hypotheses, research plans, assay methods for use of the biospecimens, and a formal statistical analysis plan with adequate power justification will be submitted to and reviewed by CTEP.

Correlative Genomic Studies of B-Lineage ALL.

11.6.1 Hypotheses:

11.6.1.1

a) Develop an improved, clinically useful molecular classification of B-ALL, identify more accurate biomarkers that could be used to further personalize therapy in future clinical trials, and identify the molecular features associated with disease relapse. b) Correlate novel findings with established prognostic parameters, such as karyotypes and MRD levels and c) Compare findings in E1910 with those published from E2993.

11.6.1.2

Two of the major challenges in improving the therapeutic outcome for patients with ALL are i) lack of diagnostic markers able to predict risk of relapse to specific therapeutic regimens, and ii) lack of understanding of disease biology, impeding the development of specific targeted therapy agents. It is currently accepted by leaders in the leukemia field that the best way to capture the molecular pathophysiology of leukemias and address these two issues is through using advanced microarray profiling methods (see report of the NCI think tank on molecular targets in lymphoid malignancies = http://cancermeetings.org/ThinkTank/Think_Tank_Summary_Online.pdf). The NCI think tank recommended that all patients enrolled in cooperative group studies be studied in this way. The reason for this recommendation is that leukemia cells are profoundly altered from the genetic and epigenetic standpoints. These alterations collectively determine the biological phenotype of the cell, which can best be captured through these kinds of analysis.

11.6.2 Correlative Study Design:

Integrated genomic and epigenomic profiling of patients enrolled in E1910 will be performed, both at diagnosis and relapse. Specifically, leukemia blast cells will be subjected to exome capture and sequencing, RNA-seq and DNA methyl-seq. These three methodologies are performed high throughput and inexpensively using bar-coding and Illumina HiSeq2000 technology. Diagnostic samples will also be assessed by ChIP-seq to determine the impact of histone modifications on leukemia cell transcriptional profiling. This is important since a number of ALL oncoproteins contain or associate with histone modifying enzymes (e.g. MLL, TEL-AML, etc). The technology is available and implemented in the laboratories of two of the members of the ECOG-ACRIN Leukemia Laboratory Committee (A. Melnick and R. Levine). These methods require very little in the way of starting material and can be readily performed in as little as ten million cells. T cells will be selected from the bone marrow or peripheral blood specimens as a source of control DNA or alternatively, buccal cell DNA will be used. Drs. Melnick and Levine have previously performed more limited integrative genomics studies using microarrays in over 400 ALL and 800 AML patients (in the ECOG E1900, E1905, and E2993 clinical trials, as well as from patients enrolled in COG, St Jude's and HOVON clinical trials). These previous studies, which also included multiplatform analysis demonstrated that such approaches are feasible in ECOG-ACRIN and other clinical trial specimens, as published [70-77]. Although highly informative these previous studies could not capture the depth of information that is uncovered through deep sequencing strategies. The results of the current correlative study will be crucial to the design of subsequent studies and for the development of targeted therapy approaches that could subsequently be translated to the clinic. Once analyzed, the data will be placed on the Melnick lab sequencing and genomics visualization server as a public service to ECOG-ACRIN and non-ECOG-ACRIN investigators. The data will provide critical explanations as to why certain patients respond and others do not on this clinical trial, by providing indepth molecular mapping of the genomic and epigenomic circuitry of these tumors. Upon publication, all genomic and epigenomic data will be posted on publically accessible sites, such as the GO database, as routinely done by ECOG-ACRIN Leukemia Laboratory investigators.

This analysis will be performed by Dr. Ari Melnick of Weill Cornell Medical College and Dr. Ross Levine of Memorial Sloan Kettering Cancer Center.

11.7 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.

12. Electronic Data Capture

Please refer to the E1910 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL negative B lineage Acute Lymphoblastic Leukemia in Adults

Appendix II

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill.

If you forget, the missed pills will not be taken later.

Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

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CYCLOPHOSPHAMIDE

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
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DEXAMETHASONE

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
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6-MERCAPTOPURINE (take at bedtime on an empty stomach 1 hour before or 2 hours after food and/or milk products)

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
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LEUCOVORIN

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METHOTREXATE

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
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PREDNISONE

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
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Appendix III

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CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available as described in the IP Option to Collaborator to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Blinatumomab, or within
Rev. Add16 28 days of the female patient's last dose of Blinatumomab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS)

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if

the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Rev. Add14 ***Reporting a Pregnancy Loss***

A pregnancy loss is defined in CTCAE as "A death in utero."

It must be reported via CTEP-AERS as Grade 4 "Pregnancy loss" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions".

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Rev. Add14 ***Reporting a Neonatal Death***

A neonatal death is defined in CTCAE as "A death occurring during the first 28 days after birth" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to Blinatumomab must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*Death Neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional
Rev. Add16 medical information to CTEP (301-897-7404). This form is available on CTEP's website

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix VI

Writing Sample Page

Subject ID _____

Instructions for the Subject: Enter the date and time of day. Rewrite the phrase listed.

Study Day	Date	Time	***Sweet as apple pie***	Study Staff or ACS-Initial & Date

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Appendix VII

Clinical Site Management of Out-patient Treatment Using CTEP-supplied Blinatumomab

- PREPARED IV INFUSION BAGS MAY NOT BE CHANGED BY THE STUDY SUBJECT
- PREPARED INFUSION BAGS OR INTACT VIALS MUST NOT BE TRANSPORTED TO ANOTHER LOCATION BY THE STUDY SUBJECT

AGENT PREPARATION AND ADMINISTRATION OPTIONS

1. Prepare all out-patient infusion bags at the registering/treating NCTN Network institution. Study subjects should return to the registering/treating institution for all infusion bag changes.
2. For study subjects that cannot return to the registering/treating institution every 48-hours for infusion bag exchanges, the next preference would be for **another NCTN Network institution that is participating on the trial and is closer to the subject's home take over** responsibility for the study subject's protocol participation. In such cases, transfer of the subject's protocol registration to another participating investigator and institution should be considered.
3. If transferring the subject's protocol registration to another participating investigator and trial site within the NCTN Network is not feasible, use of **a local outpatient infusion center** could be considered.
    a. First preference would be for all infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container to the local out-patient infusion center.
    b. The prepared infusion bags are stored at the local outpatient infusion center. The infusion center would perform each infusion bag change.
    c. If the local outpatient infusion center will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the local outpatient infusion center, with infusion bags prepared and administered by the local outpatient infusion center staff.
    d. In either case, the local outpatient infusion center would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).
    e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the local infusion center by registering/treating institution or local infusion center staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the local infusion center via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container.
4. If an outpatient infusion center is not an option, use of a **home health care service** provider can be considered.
    a. The first preference would be for all outpatient infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container to the servicing home health care agency.

b. The prepared infusion bags are stored by the home health care agency and each individual infusion bag transported to the subject's home by the home health care service nursing staff under refrigerated storage conditions for each infusion bag change.

c. If home health care agency will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the home health care agency, with infusion bags prepared and administered by the home health care agency staff.

d. In either case, the home health care agency would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the home health care agency by registering/treating institution or home health care agency staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the home health care agency via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container

5. If all options above are not feasible, shipping the prepared infusion bags directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable.

a. The prepared infusion bags are to be shipped in a 2° to 8°C pre-qualified shipping container containing one infusion bag per box. Example, if you are making 2 x 48 hour infusion bags, each infusion bag will be shipped in a separate 2° to 8°C pre-qualified shipping container. The number of infusion bags that may be prepared and shipped is dependent on the duration the shipping container used is qualified to maintain 2° to 8°C temperature.

b. Patients should NOT open the shipping container upon arrival. Shipping containers are to be stored in a secured area away from reach of children or pets.

c. Shipping containers must only be opened by the home health care service staff at the time of the infusion bag change. Only one shipping container should be opened at a time. If cold-chain management of the prepared infusion bag has been interrupted by opening of the shipping container or storage of the prepared infusion bag in the shipping container exceeds the duration of the qualified time the container will maintain 2° to 8°C temperature, the infusion bag should not be used.

The home health care service staff should immediately contact the registering/treating institution site pharmacy as indicated on the shipment form. Within 1 business day, the registering/treating institution site should inform the ECOG-ACRIN Operations office at (617) 632-3610 to report such occurrences. ECOG-ACRIN should notify PMB/CTEP at PMBafterhours@mail.nih.gov of all such occurrences of prepared, unusable infusion bags shipped to a patient's home within 1 business day of receiving notification from the registering/treating institution.

d. Form documenting the time of packaging in the shipping container, duration of time the container will maintain 2° to 8°C temperature and verification that cold-chain management was maintained prior to administration must be included in each shipping container and returned to registering/treating institution for documentation purposes.

e. Home health care service staff is to use GCP guidelines.

EVALUATION OF POTENTIAL SATELLITE PHARMACY SITES

When the registering/treating institution is considering use of a local infusion center or home health care agency as a satellite pharmacy, the following must be assessed by the registering/treating institution in relation to the suitability of the local infusion center or home health care agency:

- Ability to appropriately store(temperature and security) the intact agent vials and prepared infusion bags
- Ability to provide documentation of controlled and monitored temperature storage conditions while the IND agent is in the local infusion center or home health care agency possession
- Availability of appropriately trained staff to prepare doses in compliance with USP <797> guidelines and the protocol, to label infusion bags according to the protocol instructions and to store agent doses under appropriate controlled temperature conditions.
- Availability of appropriately trained staff to administer the prepared doses and perform the infusion bag changes according to the protocol
- Methods for proper disposal of the waste, empty vials, IV bags, etc. are inplace
- Plan for return of unused intact vials to the registering/treating institution is inplace
- Source documentation to confirm agent administration must be maintained by the local infusion center or home health care agency and must be provided to the registering/treating institution for incorporation into the patient's medical/research records and for audit purposes
- Plan for handling missed doses is in place
- Agent accountability must be maintained via use of the NCI Drug Accountability Record Form (DARF). The originating site must keep a Control DARF and the local infusion center or home health care agency would be required to maintain a Satellite DARF if receiving and storing supplies of intact vials or receiving and storing infusion bags prepared by the registering/treating institution. Maintenance of a Satellite DARF is not required by home health care agency staff for prepared infusions bags shipped to the subject's home.
- The DARF must be provided to the registering/treating institution for record keeping purposes and audits
- Documentation of IRB coverage for the protocol must be maintained. The IRB of record for the site must be informed that the study subject may receive therapy administered by a non-research site (i.e., the local infusion center or home health care agency).

TRAINING FOR ALL PARTICIPATING SITES

The Lead Network Group for the trial must work with participating sites to:

a. Implement a training process for participating NCTN Network sites regarding blinatumomab preparation and administration. Documentation of participating site training must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial.

b. Develop a plan for participating NCTN Network sites to assess local outpatient infusion centers or home health care agency for patient treatment if required and document training of such sites

c. Have a training manual available for local outpatient infusion centers or home health care agencies on the clinical trial, appropriate agent preparation, handling and administration requirements and appropriate record keeping requirements

d. Create a definitive written communication plan for use between registering/treating institution and the local outpatient infusion centers or home health care agency on an ongoing basis during subject's treatment regimen, including emergency contact information for the registering/treating institution and investigator

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Appendix VIII

Shipment of blinatumomab IV Bag from Site/Pharmacy to Patient's Home

To be completed by Site/Pharmacy:

From: (Investigator Name, Address)	**To Patient:** (Patient Initials, Study ID No) _____ ; _____	**Protocol No.:**
Site Pharmacy contact	— — —	

Prepare shipment of IV bag at 2°C to 8°C in validated/pre-qualified insulated shipper as per manufacturer instructions (see shipping container instructions). Please take care to use the applicable instructions for summer or winter package preparation, respectively.

IV Bag number	**Date of packaging** [DD/MMM/YYYY]	**Time of packaging** [hh:mm]	**pa ck**

Please tick the boxes and fill in the information below when preparing the IV bag shipment!

- ☐ **Validated/pre-qualified shipping container duration of time 2°C to 8°C temperature is maintained: _____ hours**
- ☐ **Cooling elements for provided box used according to manufacturer's instruction**

Confirmed by:_____ _____
(print name, signature) (date)

To be completed by Ambulant/Home Care Service Provider:

Shipment box unopened and content intact? **YES** ☐

NO ☐

IF NO, please comment _____

Date and time shipment box opened: _____ _____
(date) (time)

Confirmed by: _____ _____
(print name, signature) Amb. Care Service (date)

NOTE: If content is not intact, please do not use IV bag and inform site pharmacy immediately! If time box opened minus time of packaging exceeds the time duration the shipping container maintains 2°C to 8°C, please do not use IV bag and inform site pharmacy immediately!

Rev. 8/17

Appendix IX

Mercaptopurine Dosing Guidelines

Rev. 2/18

60 mg/m2 DOSES OF MERCAPTOPURINE

Body Surface Area (m²)	Daily Dose for 7 days* (1 tablet = 50 mg)	
1.26 - 1.30	1 ½ tab / d x 6; 2 tab / d x 1	(550 mg/wk)
1.31 - 1.36	2 tab / d x 2; 1½ tab / d x 5	(575 mg/wk)
1.37 - 1.43	2 tab / d x 3; 1½ tab / d x 4	(600 mg/wk)
1.44 - 1.49	2 tab / d x 4; 1½ tab / d x 3	(625 mg/wk)
1.50 - 1.55	2 tab / d x 5; 1½ tab / d x 2	(650 mg/wk)
1.56 - 1.61	2 tab / d x 6; 1½ tab / d x 1	(675 mg/wk)
1.62 - 1.67	2 tab / d x 7	(700 mg/wk)
1.68 - 1.73	2 tab / d x 6; 2½ tab / d x 1	(725 mg/wk)
1.74 - 1.79	2½ tab / d x 2; 2 tab / d x 5	(750 mg/wk)
1.80 - 1.85	2½ tab / d x 3; 2 tab / d x 4	(775 mg/wk)
1.86 - 1.91	2½ tab / d x 4; 2 tab / d x 3	(800 mg/wk)
1.92 - 1.97	2½ tab / d x 5; 2 tab / d x 2	(825 mg/wk)
1.98 - 2.03	2½ tab / d x 6; 2 tab / d x 1	(850 mg/wk)
2.04 – 2.09	2 ½ tab / d x 7	(875 mg/wk)
2.10 – 2.15	2 ½ tab / d x 6; 3 tab / d x 1	(900 mg/wk)
2.16 – 2.21	3 tab / d x 2; 2 ½ tab x 5	(925 mg/wk)
2.22 – 2.27	3 tab / d x 3; 2 ½ tab / d x 4	(950 mg /wk)
2.28 – 2.33	3 tab / d x 4; 2 ½ tab / d x 3	(975 mg/wk)
2.34 – 2.39	3 tab / d x 5; 2 ½ tab / d x 2	(1,000 mg/wk)
2.40 – 2.45	3 tab / d x 6; 2 ½ tab / d x 1	(1,025 mg/wk)
2.46 – 2.51	3 tab / d x 7	(1,050 mg/wk)

* The 7-day daily dose refers to 7-day cycles within continued daily administration (e.g., during induction, consolidation, and throughout maintenance). The doses should be taken in the evening, at least one hour after eating.

Rev. 2/18

75 mg/m2 DOSES OF MERCAPTOPURINE

Body Surface Area (m²)	Daily Dose for 7 days* (1 tablet = 50 mg)	
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	(650 mg/wk)
1.30 - 1.34	2 tab / d x 6; 1½ tab / d x 1	(675 mg/wk)
1.35 - 1.39	2 tab / day	(700 mg/wk)
1.40 - 1.44	2 tab / d x 6; 2½ tab / d x 1	(725 mg/wk)
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	(750 mg/wk)
1.50 - 1.54	2 tab / d x 4; 2½ tab / d x 3	(775 mg/wk)
1.55 - 1.59	2½ tab/ d x 4; 2 tab / d x 3	(800 mg/wk)
1.60 - 1.64	2½ tab/ d x 5; 2 tab / d x 2	(825 mg/wk)
1.65 - 1.69	2½ tab/ d x 6; 2 tab / d x 1	(850 mg/wk)
1.70 - 1.74	2½ tab/ d x 7	(875 mg/wk)
1.75 - 1.79	2½ tab/ d x 6; 3 tab / d x 1	(900 mg/wk)

	1.80 - 1.84	2½ tab/ d x 5; 3 tab / d x 2	(925 mg/wk)
	1.85 – 1.89	2½ tab/ d x 4; 3 tab / d x 3	(950 mg/wk)
	1.90 – 1.94	3 tab/ d x 4; 2½ tab / d x 3	(975 mg/wk)
	1.95 – 1.99	3 tab/ d x 5; 2½ tab / d x 2	(1000 mg/wk)
Rev. Add16	2.00 – 2.04	3 tab/ d x 6; 2½ tab / d x 1	(1,025 mg/wk)
	2.05 – 2.09	3 tab/ d x 7	(1,050 mg/wk)
	2.10 – 2.14	3 tab/ d x 6; 3½ tab / d x 1	(1,075 mg/wk)
	2.15 – 2.19	3 tab/ d x 5; 3½ tab / d x 2	(1,100 mg/wk)
	2.20 – 2.24	3 tab/ d x 4; 3½ tab / d x 3	(1,125 mg/wk)
	2.25 – 2.29	3 ½ tab/ d x 4; 3 tab / d x 3	(1,150 mg/wk)
	2.30 – 2.34	3 ½ tab/ d x 5; 3 tab / d x 2	(1,175 mg/wk)
	2.35 – 2.39	3 ½ tab/ d x 6; 3 tab / d x 1	(1,200 mg/wk)
	2.40 – 2.44	3 ½ tab/ d x 7	(1,225 mg/wk)
	2.45 – 2.49	3 ½ tab/ d x 6; 4 tab / d x 1	(1,250 mg/wk)
	2.50 – 2.54	3 ½ tab/ d x 5; 4 tab / d x 2	(1,275 mg/wk)

* The 7-day daily dose refers to 7-day cycles within continued daily administration (e.g., during induction, consolidation, and throughout maintenance). The doses should be taken in the evening, at least one hour after eating.

(Taken and adapted from CALGB 10403)