A Phase II Study of Inotuzumab Ozogamicin Followed by Blinatumomab for Ph-negative CD22-positive B-lineage Acute Lymphoblastic Leukemia in Newly Diagnosed Older Adults or Adults with Relapsed or Refractory Disease

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Key Eligibility Criteria (see Section 3.0)

Cohort 1 and Cohort 2 Patients:

- Ph-negative, CD22-positive precursor B-cell acute lymphoblastic leukemia
- No active CNS leukemia
- No known or suspected testicular involvement by leukemia
- Not pregnant or nursing
- ECOG Performance Status: 0-2
- No unstable cardiac disease within 6 months of registration
- No LVEF < 45% or NYHA stage III or IV CHF
- No history of clinically significant ventricular arrhythmia, unexplained non-vasovagal syncope, or chronic bradycardic states unless a permanent pacemaker has been implanted.
- Patients with known HIV infection, hepatitis B virus (HBV), and/or history of hepatitis C virus (HCV) are allowed if they meet specified criteria (see Section 3.3.4)
- No history of clinically relevant neurologic disorder
- No prior additional malignancy (see Section 3.3.5 for exceptions)
- No history of chronic liver disease including cirrhosis or SOS/VOD of the liver
- No uncontrolled infection
- Total bilirubin ≤ 1.5 x ULN
- AST/ALT ≤ 2.5 x ULN
- Calculated creatinine clearance ≥ 40 mL/min
- QTcF ≤ 470 msec

Cohort 1 Patients Only:

- Age ≥ 60 years
- No prior therapy for ALL except a single dose of intrathecal chemotherapy, corticosteroids, hydroxyurea, and/or leukapheresis to reduce peripheral blast count and prevent ALL complications. Allowed therapy may be administered for no more than 14 days and must be completed ≥ 24 hours before starting protocol therapy.
- No plan for allogeneic or autologous hematopoietic cell transplantation (HCT)

Cohort 2 Patients Only:

- Age ≥ 18 years
- Relapsed or refractory disease in salvage 1 or 2
- No isolated extramedullary relapse
- Prior allogeneic HCT permitted. If prior allogeneic HCT, then patients must have completed transplantation ≥ 4 months prior to registration, have no evidence of GvHD, and have completed immunosuppressive therapy ≥ 30 days prior to registration.
- No prior treatment with CD22- or CD19-directed therapy. Prior treatment with rituximab must be completed ≥ 14 days prior to registration. Prior treatment with other monoclonal antibodies must be completed ≥ 6 weeks prior to registration.
- Prior treatment for ALL must be completed ≥ 14 days prior to registration with the following exceptions: hydroxyurea, corticosteroids, 6-mercaptopurine, methotrexate, vincristine, and/or leukapheresis to reduce circulating absolute lymphoblast count to ≤ 10,000/μL or prevent complications related to ALL are allowed but must be completed ≥ 24 hours prior to the start of protocol therapy.
- Resolution of acute non-hematologic toxicities of prior therapy to CTCAE v5.0 grade ≤ 1
- Peripheral blood absolute lymphoblast count ≤ 10,000/μL (treatment allowed as above to reduce blasts)

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Confirmation of Tolerability (see Section 7.1)

As of Update #03, the Confirmation of Tolerability Portion has been completed.

To ensure safety and tolerability of the sequential dosing on inotuzumab ozogamicin followed by blinatumomab, we will treat the first 6 patients registered to either cohort to evaluate and confirm the tolerability of this regimen when one or two courses of inotuzumab ozogamicin is/are followed by blinatumomab given for one or two courses. Here we will use the established rule for a tolerable dose as defined through the rolling 6 phase I design, where if at most one of these 6 patients has a dose-limiting toxicity (DLT) event (see Section 13.6), then we will consider this tolerable and move on to full accrual and treatment through the phase II study.

The safety lead-in monitoring period will be from Day 1 through Day 28 of the first blinatumomab course (Course II of consolidation therapy). For this study, a DLT is defined as being unable to complete the monitoring period from Day 1 through Day 28 of Course II blinatumomab consolidation therapy or inability to restart blinatumomab within 14 days of an interruption during Course II due to toxicity (i.e. not disease progression or removal from study for transplant or patient/physician choice) thought by the investigator to be possibly, probably, or definitely related to the combination of inotuzumab ozogamicin followed by blinatumomab and not discontinuation due to known toxicities (please see package insert for list of known toxicities) of either individual drug given as monotherapy. Reasons for discontinuing therapy are outlined in Section 12.0.

If ≥2 DLTs attributable to the combination of inotuzumab ozogamicin followed by blinatumomab occur in the first 6 patients within the first 28 days of receiving blinatumomab, a meeting of investigators to review toxicity data will occur to determine if further study of the combination is warranted with the possibility of exploring lower dose levels or different sequencing of the agents.

If the tolerability of inotuzumab ozogamicin followed by blinatumomab is confirmed, full accrual to this phase II trial will continue.

For the confirmation of tolerability portion of the study, patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient.

Once a site logs into the OPEN system during the confirmation of tolerability portion of the study, the number of slots available will be listed.

Investigators enrolling patients during the confirmation of tolerability portion of the study will be required to participate in an every other week conference call to discuss study concerns, patient progress, and adverse events.

Phase II (see Section 7.2, Section 7.3, and Section 7.4)
Cohort 1: No prior therapy within 2 weeks except corticosteroids, hydroxyurea, leukapheresis, and/or a single dose of intrathecal chemotherapy. Allowed therapy may be administered for ≤ 14 days, and must be completed ≥ 24 hours prior to the initiation of protocol therapy.

Cohort 2: No prior therapy within 2 weeks except treatment with corticosteroids, hydroxyurea, 6-mercaptourine, methotrexate, vincristine, and/or leukapheresis to control high lymphoblast count; allowed therapy must be completed ≥ 24 hours prior to the initiation of protocol therapy.

The intent of this study is to administer the prescribed therapy as rapidly and safely as possible without unnecessary delays. Please see Section 7.2 for additional supportive care information prior to the initiation of treatment. Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan. If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Patient Enrollment Pathway – Cohort 1

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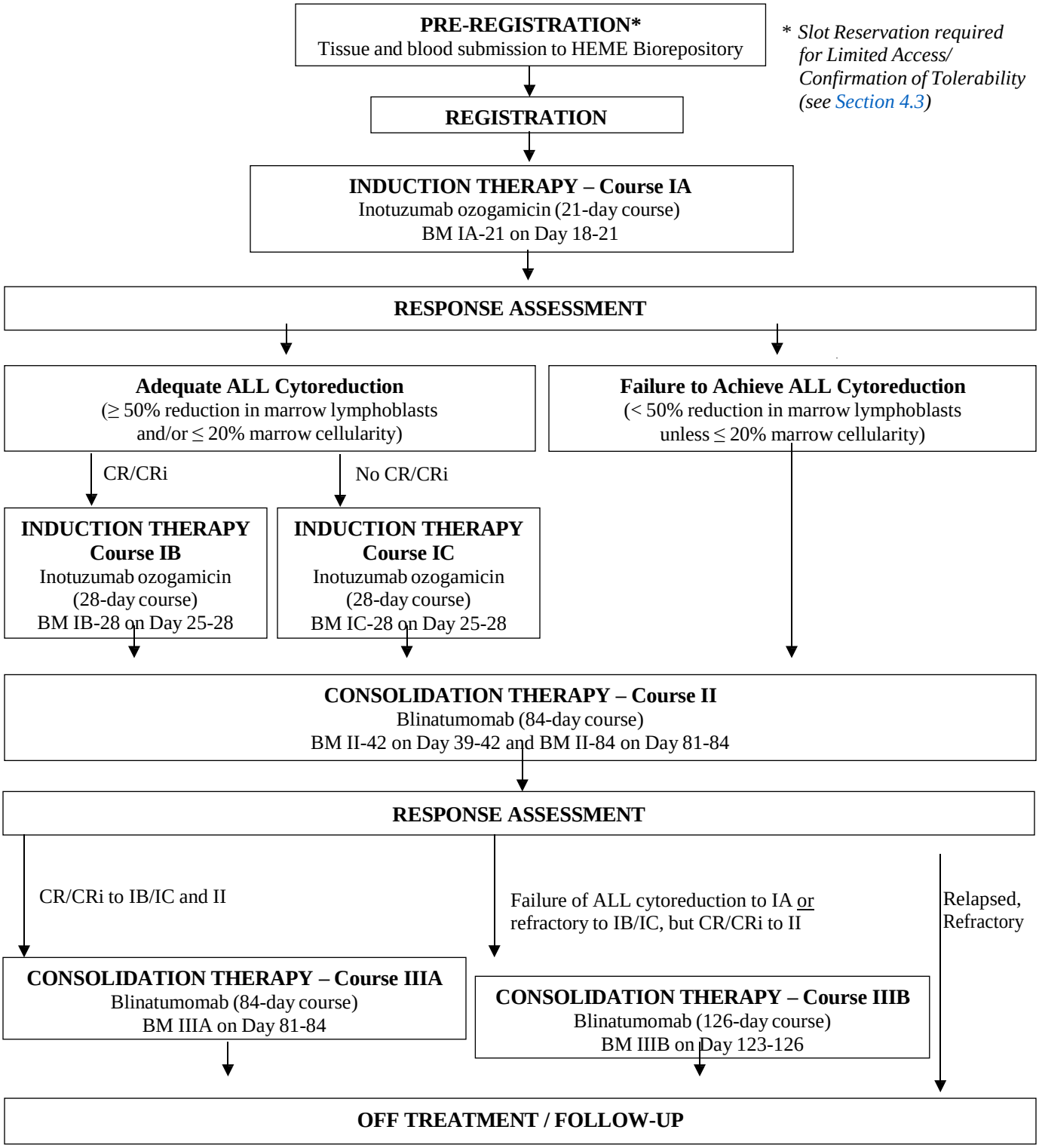
Cohort 1: Adults ≥ 60 years with newly diagnosed B-lineage ALL



BM = bone marrow aspiration and peripheral blood; CR = complete remission; CRi = complete remission with incomplete count recovery.

Patient Enrollment Pathway – Cohort 2

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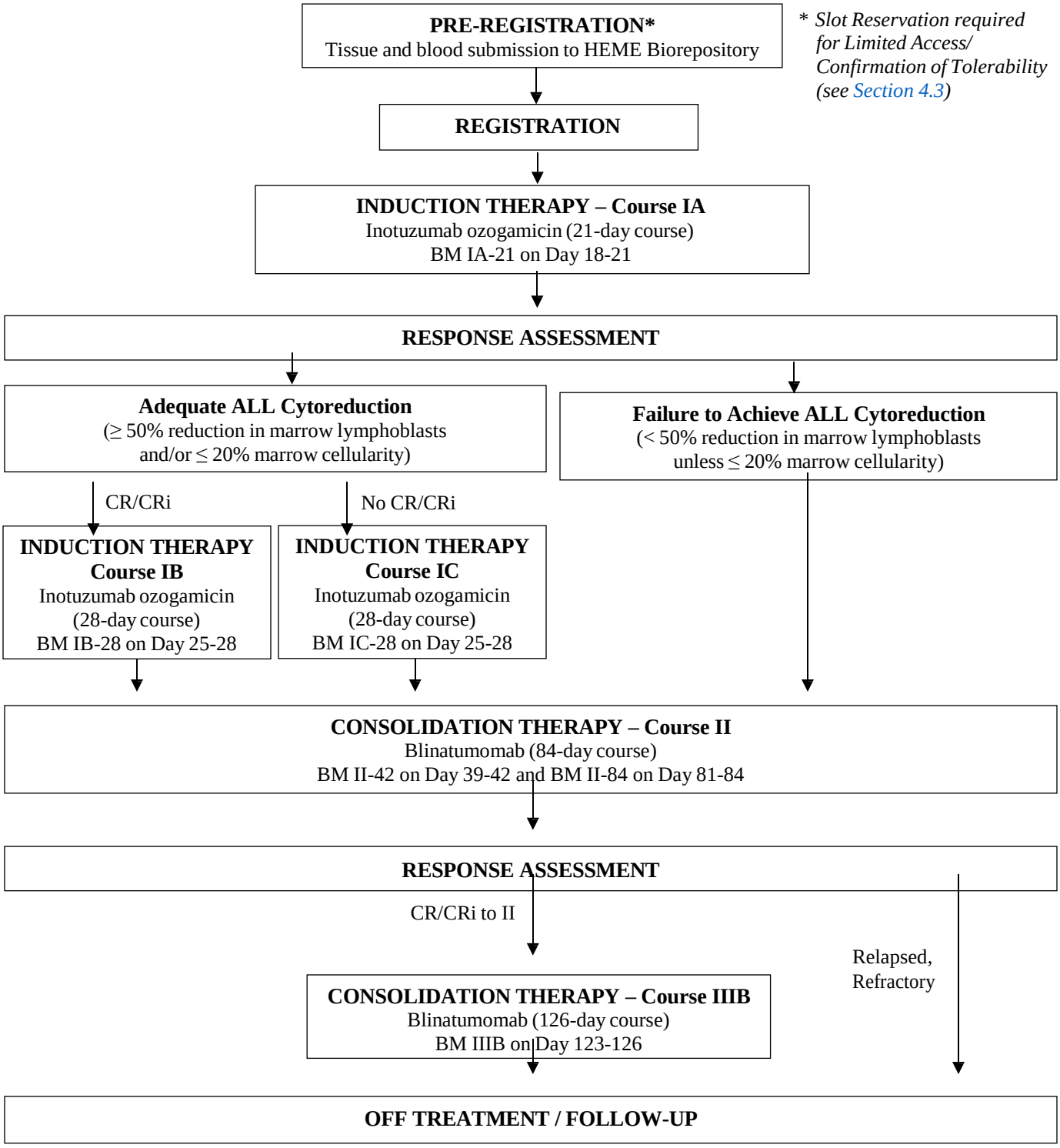
Cohort 2: Adults ≥ 18 years with relapsed or refractory B-lineage ALL



NOTE: Cohort 2 patients may proceed to allogeneic HCT any time after a CR/CRi; follow-up per Section 5.0.

BM = bone marrow aspiration and peripheral blood; CR = complete remission; CRi = complete remission with incomplete count recovery.

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See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041703-PP1, then collect and submit specimens as required per Section 6.2.

Induction Therapy: Course IA (see Section 7.3)

All patients in both Cohort 1 and Cohort 2 receive **Course IA** of induction therapy.

	INO							INO							INO						
	IT MTX																				
																		▪ BM IA-21 →			
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

INO — Inotuzumab ozogamicin 0.8 mg/m^2/day IV on Day 1 and inotuzumab ozogamicin 0.5 mg/m^2/day IV on Days 8 and 15 of a 21-day course. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent per institutional standard of care). Monitor patients closely during and for at least 1 hour after the end of the infusion for the potential onset of infusion-related reactions, including symptoms such as fever, chills, rash or breathing problems. If an infusion-related reaction occurs, refer to guidelines in Section 7.1 and Section 8.1.

IT MTX — Intrathecal (IT) methotrexate 15 mg on Day 1 (+/- 3 days) unless given prior to registration, then omit. Addition of intrathecal hydrocortisone is allowed per institutional practice.

BM — Bone marrow aspirate, bone marrow biopsy, and peripheral blood specimens must be obtained for all patients between Day 18 and Day 21 of Course IA of induction therapy to assess induction response and minimal residual disease; see Section 7.3.

See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041703-PP1, then collect and submit specimens as required per Section 6.2.

Induction Therapy: Course IB (see Section 7.3)

Cohort 1 and Cohort 2 patients with adequate ALL cytoreduction and with a CR/CRi at the end of **Course IA** of induction therapy (BM IA-21) will receive **Course IB** of induction therapy.

Adequate ALL cytoreduction is defined as ≥ 50% reduction in bone marrow lymphoblasts from the baseline bone marrow aspirate and/or ≤ 20% marrow cellularity.

Course IB should start within 7 days of completing **Course IA** or when the following treatment parameters have been met:

- Recovery to grade ≤ 1 or baseline non-hematologic inotuzumab-ozogamicin-related toxicity
- Serum AST, ALT ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN (or if total bilirubin elevated due to ALL or Gilbert's disease, then serum total bilirubin ≤ 2.0 x ULN)
- Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 40 mL/min
- ANC ≥ 1 x 10^6/mcL (please refer to Section 8.2.1.3 for complete details)
- Platelets ≥ 50 x 10^6/mcL (please refer to Section 8.2.1.3 for complete details)

If a patient does not meet the treatment parameters for **Course IB** within 14 days of completing **Course IA**, then the site should contact the Study Chair.

If a patient does not meet the treatment parameters for **Course IB** within 28 days of completing **Course IA** due to inotuzumab-ozogamicin-related toxicity, then site should contact the Study Chair, permanently discontinue inotuzumab ozogamicin, and the patient should receive **Course II** of consolidation therapy.

	INO							INO							INO						
	IT MTX																				
																		▪ BM IB-28 →			
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	…	25	26	27	28

INO — Inotuzumab ozogamicin 0.5 mg/m^2/day IV on Days 1, 8, and 15 of a 28-day course. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent per institutional standard of care). Monitor patients closely during and for at least 1 hour after the end of the infusion for the potential onset of infusion-related reactions, including symptoms such as fever, chills, rash or breathing problems. If an infusion-related reaction occurs, refer to guidelines in Section 7.1 and Section 8.1.

IT MTX — Intrathecal (IT) methotrexate 15 mg on Day 1 (+/- 3 days). Addition of intrathecal hydrocortisone is allowed per institutional practice.

BM — Bone marrow aspirate, bone marrow biopsy, and peripheral blood specimens must be obtained for all patients between Day 25 and Day 28 of Course IB of induction therapy to assess induction response and minimal residual disease; see Section 7.3.

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See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041703-PP1, then collect and submit specimens as required per Section 6.2.

Induction Therapy: Course IC (see Section 7.3)

Cohort 1 and Cohort 2 patients with adequate ALL cytoreduction but without a CR/CRi at the end of **Course IA** of induction therapy (BM IA-21) will receive **Course IC** of induction therapy.

Adequate ALL cytoreduction is defined as ≥ 50% reduction in bone marrow lymphoblasts from the baseline bone marrow aspirate and/or ≤ 20% marrow cellularity.

Course IC should start within 7 days of completing **Course IA** or when the following treatment parameters have been met:

- Recovery to grade ≤ 1 or baseline non-hematologic inotuzumab-ozogamicin-related toxicity
- Serum AST, ALT ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN (or if total bilirubin elevated due to ALL or Gilbert's disease, then serum total bilirubin ≤ 2.0 x ULN)
- Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 40 mL/min

If a patient does not meet the treatment parameters for **Course IC** within 14 days of completing **Course IA**, then the site should contact the Study Chair.

If a patient does not meet the treatment parameters for **Course IC** within 28 days of completing **Course IA** due to inotuzumab-ozogamicin-related toxicity, then site should contact the Study Chair, permanently discontinue inotuzumab ozogamicin, and the patient should receive **Course II** of consolidation therapy.

	INO							INO							INO						
	IT MTX																				
																		▪ BM IC-28 →			
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	…	25	26	27	28

INO — Inotuzumab ozogamicin 0.8 mg/m^2/day IV on Day 1 and inotuzumab ozogamicin 0.5 mg/m^2/day IV on Days 8 and 15 of a 28-day course. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent per institutional standard of care). Monitor patients closely during and for at least 1 hour after the end of the infusion for the potential onset of infusion-related reactions, including symptoms such as fever, chills, rash or breathing problems. If an infusion-related reaction occurs, refer to guidelines in Section 7.1 and Section 8.1.

IT MTX — Intrathecal (IT) methotrexate 15 mg on Day 1 (+/- 3 days). Addition of intrathecal hydrocortisone is allowed per institutional practice.

BM — Bone marrow aspirate, bone marrow biopsy, and peripheral blood specimens must be obtained for all patients between Day 25 and Day 28 of Course IC of induction therapy to assess induction response and minimal residual disease; see Section 7.3.

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See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041703-PP1, then collect and submit specimens as required per Section 6.2.

Consolidation Therapy – Course II (see Section 7.4)

All patients in both Cohort 1 and Cohort 2 will receive **Course II** of consolidation therapy.

At minimum, patients should be hospitalized for blinatumomab administration on Days 1-9, Days 43-45, and for at least 2 days for any mid-course restarts after a drug interruption lasting ≥ 4 hours.

Course II should start within 7 days of completion of **Course IA**, **Course IB**, or **Course IC** as applicable or when the following treatment parameters have been met:

- Recovery to grade ≤ 1 or baseline non-hematologic inotuzumab-ozogamicin-related toxicity
- ANC ≥ 1 x 10^6/mcL if patient in CR/CRi
- Platelets ≥ 50 x 10^6/mcL if patient in CR/CRi

If a patient does not meet the treatment parameters for **Course II** within 14 days of completing prior course, then the site should contact the Study Chair.

	BLN →					BLN →								*Rest* →							
	IT MTX									IT MTX				IT MTX							
																		▪ BM II-42 →			
Day	1	2	…	6	7	8	9	…	14	15	16	…	28	29	30	…	38	39	40	41	42

	BLN →													*Rest* →							
	IT MTX									IT MTX				IT MTX							
																		▪ BM II-84 →			
Day	43	44	45	46	47	48	…	55	56	57	58	…	70	71	72	…	80	81	82	83	84

BLN — Blinatumomab 9 mcg/day as **fixed dose** for weight ≥ 45 kg (or 5 mcg/m^2/day as **BSA-based dose** if weight < 45 kg, not to exceed 9 mcg/day) continuous IV (CIV) on Days 1-7 followed by blinatumomab 28 mcg/day as **fixed dose** for weight ≥ 45 kg (or 15 mcg/m^2/day as **BSA-based dose** if weight < 45 kg, not to exceed 28 mcg/day) CIV on Days 8-28 and Days 43-70 of an 84-day course; Days 29-42 and Days 71-84 are considered *rest* days off CIV blinatumomab therapy. Day 43 of blinatumomab therapy may be delayed up to 3 days; if delayed, the start day of blinatumomab therapy should be counted as Day 43. Premedicate with dexamethasone 20 mg intravenously 1 hour prior to starting blinatumomab on Days 1, 8, and 43, prior to any step-up dose, or when restarting infusion after an interruption of ≥ 4 hours.

IT MTX — Intrathecal (IT) methotrexate 15 mg on Days 1, 15, 29, 43, 57, and 71 (+/- 3 days). Addition of intrathecal hydrocortisone allowed per institutional practice.

BM — Bone marrow aspirate, bone marrow biopsy, and peripheral blood specimens must be obtained for all patients between Day 39 and Day 42 and between Day 81 and Day 84 of Course II of consolidation therapy to assess response and minimal residual disease; see Section 7.4.

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See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041703-PP1, then collect and submit specimens as required per Section 6.2.

Consolidation Therapy – Course IIIA (see Section 7.4)

Cohort 1 patients with a CR/CRi at the end of either **Course IB** (BM IB-28) or **Course IC** (BM IC-28) **and** with a CR/CRi after **Course II** (BM II-84) will receive **Course IIIA** of consolidation therapy.

Course IIIA should start within 7 days of completing **Course II** or when the following treatment parameters have been met:

- Recovery to grade ≤ 1 or baseline non-hematologic treatment-related toxicity
- ANC ≥ 1 x 10^6/mcL
- Platelets ≥ 50 x 10^6/mcL

If a patient does not meet the treatment parameters for **Course IIIA** within 14 days of completing prior course, then the site should contact the Study Chair.

	BLN →															*Rest* →					
	(IT MTX)																				
Day	1	2	3	4	5	6	…	13	14	15	16	…	26	27	28	29	30	…	40	41	42

	BLN →														*Rest* →					
																	▪ BM IIIA-84 →			
Day	43	44	45	46	47	…	53	54	55	56	…	68	69	70	71	…	81	82	83	84

BLN — Blinatumomab 28 mcg/day as **fixed dose** for weight ≥ 45 kg (or 15 mcg/m^2/day as **BSA-based dose** if weight < 45 kg, not to exceed 28 mcg/day) continuous IV (CIV) on Days 1-28 and Days 43-70 of an 84-day course; Days 29-42 and Days 71-84 are considered *rest* days off CIV blinatumomab therapy. Day 43 of blinatumomab therapy may be delayed up to 3 days; if delayed, the start day of blinatumomab therapy should be counted as Day 43. Premedicate with dexamethasone 20 mg intravenously 1 hour prior to starting blinatumomab on Day 1, prior to any step-up dose, or when restarting infusion after an interruption of ≥ 4 hours.

(IT MTX) — Intrathecal (IT) methotrexate 15 mg on Day 1 (+/- 3 days) for patients who did not receive Course IB/IC of therapy. Patients will receive a total of 8 IT methotrexate treatments throughout study therapy. Addition of IT hydrocortisone allowed per institutional practice.

BM — Bone marrow aspirate, bone marrow biopsy, and peripheral blood specimens must be obtained for all patients between Day 81 and Day 84 of Course IIIA of consolidation therapy to assess response and minimal residual disease; see Section 7.4.

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See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041703-PP1, then collect and submit specimens as required per Section 6.2.

Consolidation Therapy – Course IIIB (see Section 7.4)

The following patients will receive **Course IIIB** of consolidation therapy:

- Cohort 1 patients without adequate ALL cytoreduction* at the end of **Course IA** of induction therapy (BM IA-21) **but** with a CR/CRi at the end of **Course II** of consolidation therapy (BM II-84).
  *Adequate ALL cytoreduction is defined as ≥ 50% reduction in bone marrow lymphoblasts from the baseline bone marrow aspirate/biopsy and/or ≤ 20% marrow cellularity.
- Cohort 1 patients without a CR/CRi at the end of either **Course IB** (BM IB-28) or **Course IC** (BM IC-28) of induction therapy **but** with a CR/CRi at the end of **Course II** of consolidation therapy (BM II-84).
- Cohort 2 patients with a CR/CRi at the end of **Course II** of consolidation therapy (BM II-84).

Course IIIB should start within 7 days of completing **Course II** or when the following treatment parameters have been met:

- Recovery to grade ≤ 1 or baseline non-hematologic treatment-related toxicity
- ANC ≥ 1 x 10^6/mcL
- Platelets ≥ 50 x 10^6/mcL

If a patient does not meet the treatment parameters for **Course IIIB** within 14 days of completing prior course, then the site should contact the Study Chair.

(Course IIIB schema continues on the next page.)

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Consolidation Therapy – Course IIIB (continued)

	BLN →															*Rest* →					
	(IT MTX)																				
Day	1	2	3	4	5	6	…	13	14	15	16	…	26	27	28	29	30	…	40	41	42

	BLN →															*Rest* →					
Day	43	44	45	46	47	48	49	50	51	…	67	68	69	70	71	…	80	81	82	83	84

	BLN →														*Rest* →						
																		▪ BM IIIB-126 →			
Day	85	86	87	88	89	90	91	92	93	94	95	…	111	112	113	…	122	123	124	125	126

BLN — Blinatumomab 28 mcg/day as **fixed dose** for weight ≥ 45 kg (or 15 mcg/m^2/day as **BSA-based dose** if weight < 45 kg, not to exceed 28 mcg/day) continuous IV (CIV) on Days 1-28, Days 43-70, and Days 85-112 of a 126-day course; Days 29-42, Days 71-84, and Days 113-126 are considered *rest* days off CIV blinatumomab therapy. Day 43 and Day 85 of blinatumomab therapy may be delayed up to 3 days; if delayed, the start day of blinatumomab therapy should be counted as Day 43 or Day 85, respectively. Premedicate with dexamethasone 20 mg intravenously 1 hour prior to starting blinatumomab on Day 1, prior to any step-up dose, or when restarting infusion after an interruption of ≥ 4 hours.

(IT MTX) — Intrathecal (IT) methotrexate 15 mg on Day 1 (+/- 3 days) for patients who did not receive Course IB/IC of therapy. Patients will receive a total of 8 IT methotrexate treatments throughout study therapy. Addition of IT hydrocortisone allowed per institutional practice.

BM — Bone marrow aspirate, bone marrow biopsy, and peripheral blood specimens must be obtained for all patients between Day 123 and Day 126 of Course IIIB of consolidation therapy to assess response and minimal residual disease; see Section 7.4.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled diabetes mellitus which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

In addition:

- Women and men of reproductive potential should agree to two appropriate methods of birth control, with one being a barrier method, throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom).
- Drugs that prolong the QTc interval should be avoided if possible, as the study treatment can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (see Appendix II) should be discontinued or replaced with drugs that do not carry this risk if at all possible. Patients who receive potential QTc-prolonging medications (see Appendix II) should be monitored closely.

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

      Steinherz/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 ≥ 5 WBC/μL with blasts, the following algorithm should be used to define CNS disease:

          CSF WBC/CSF RBC > 2 x (Blood WBC/Blood RBC count)

Patients with known or suspected testicular involvement by leukemia are allowed provided that the patient receives concomitant scrotal/testicular radiotherapy.

- Unilateral or bilateral testicular enlargement should be assessed by ultrasound or other imaging technique. Biopsy is recommended if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass, but further assessments are per treating physician discretion.

___ **3.3.2 Not pregnant and not nursing.**

This study involves agents that have known genotoxic, mutagenic, and teratogenic effects. Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.

___ **3.3.3 ECOG Performance Status: 0-2** (see Appendix III for definitions)

___ **3.3.4 Comorbid Conditions**

No unstable cardiac disease such as myocardial infarction, angina pectoris, uncontrolled heart failure, or uncontrolled cardiac arrhythmia within 6 months of registration.

No impaired cardiac function, defined as LVEF < 45% or NYHA stage III or IV CHF.

Patients with known human immunodeficiency virus (HIV) infection are eligible if they have been on effective antiretroviral therapy with an undetectable viral load tested within 6 months of registration.

Patients with hepatitis B virus (HBV) are eligible only if they meet all the following:

- On HBV-suppressive therapy
- No evidence of active virus
- No evidence of HBV-related liver damage

3.3 Pre-registration Eligibility Criteria (Step 0)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

3.2.1 Bone Marrow and Peripheral Blood Submission for MRD Analysis

Submission of bone marrow aspirate and peripheral blood for MRD analysis is mandatory prior to registration; the bone marrow sample should be from the first aspiration (i.e. first pull). Aspirate needle should be redirected if needed to get first pull bone marrow aspirate. It should be initiated as soon as possible after pre-registration. The specimens should be sent to the HEME Biobank; see Section 6.2.

- Lumbar Puncture (Spinal Tap) and Intrathecal Methotrexate:
    - Patients may receive the Day 1 of Course IA dose of intrathecal (IT) methotrexate during the prior-to-registration lumbar puncture (or the venous line placement) to avoid a second lumbar puncture. If the dose is administered prior to registration, then systemic chemotherapy must begin within 7 days of this IT chemotherapy.

3.3 Registration Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; 2) has not been medically confirmed to be naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months); or 3) does not have medically confirmed ovarian failure.

3.3.1 Documentation of Disease

Morphologic diagnosis of precursor B-cell acute lymphoblastic leukemia (ALL) based on WHO criteria. Patients with Burkitt lymphoma/leukemia are not eligible.

CD22-positive disease defined as CD22 expression by ≥ 20% of lymphoblasts by local hematopathology evaluation.

Philadelphia chromosome/BCR-ABL1-negative ALL by cytogenetics, FISH, and/or PCR. If any test is positive for Philadelphia chromosome/BCR-ABL1, then the patient is ineligible.

No active central nervous system (CNS) leukemia (i.e. only CNS-1 disease allowed). Active CNS leukemia is defined as morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF), use of CNS-directed local treatment for active disease within 28 days prior to registration, symptomatic CNS leukemia (i.e. cranial nerve palsies or other significant neurological dysfunction) within the 28 days prior to registration, and/or known asymptomatic parenchymal CNS mass lesions; see below for additional guidance. Prophylactic intrathecal medication alone is not an exclusion.

Patients with hepatitis C virus (HCV) are eligible only if they meet all the following:

- Successfully completed complete-eradication therapy with undetectable viral load
- No evidence of HCV-related liver damage

3.3.5 Patient History

No history of clinically relevant neurologic disorder such as epilepsy, seizure, aphasia, stroke, severe brain injury, structural brain abnormality, benign brain tumor, dementia, Parkinson's disease, movement disorder, cerebellar disease, or other significant CNS abnormalities.

No prior additional malignancy (i.e. in addition to ALL) except adequately treated basal- or squamous-cell skin cancer, *in situ* cervical cancer, stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for ≥ 2 years.

No history of clinically significant ventricular arrhythmia, unexplained non-vasovagal syncope, or chronic bradycardic states such as sinoatrial block or higher degree of atrioventricular block unless a permanent pacemaker has been implanted.

No history of chronic liver disease, including cirrhosis.

No history of sinusoidal occlusion syndrome/veno-occlusive disease of the liver.

No uncontrolled infection or recent history (within 4 months prior to registration) of deep tissue infections such as fasciitis or osteomyelitis.

3.3.6 Required Initial Laboratory Values

- Total bilirubin, serum ≤ 1.5 x ULN*
- AST/ALT ≤ 2.5 x ULN
- Creatinine clearance ≥ 40 mL/min
- QTcF ≤ 470 msec

* Except in the event of: 1) Gilbert disease, in which case total bilirubin must be ≤ 2 x ULN, or 2) elevated bilirubin believed by investigator to be due to leukemic infiltration, in which case total bilirubin must be ≤ 2 x ULN.

3.3.7 Cohort 1 Patients Only:

Age ≥ 60 years.

No prior treatment for ALL except a single dose of intrathecal chemotherapy, corticosteroids, hydroxyurea, and/or leukapheresis to reduce peripheral blast count and prevent ALL complications. Allowed therapy may be administered for no more than 14 days and must be completed ≥ 24 hours prior to the initiation of protocol therapy.

No plan for allogeneic or autologous hematopoietic cell transplantation (HCT).

3.3.8 Cohort 2 Patients Only:

Age ≥ 18 years.

Relapsed or refractory disease in salvage 1 or 2.

No isolated extramedullary relapse.

Prior allogeneic HCT permitted.

Patients with prior allogeneic HCT must have completed transplantation ≥ 4 months prior to registration.

Patients with prior allogeneic HCT must have no evidence of graft-versus-host disease and must have completed immunosuppressive therapy ≥ 30 days prior to registration.

Prior treatment with inotuzumab ozogamicin, blinatumomab, other CD22-directed therapy, or other CD19-directed therapy is not allowed.

Prior treatment with rituximab must be completed ≥ 7 days prior to registration.

Prior treatment with other monoclonal antibodies must be completed ≥ 6 weeks prior to registration.

Prior treatment for ALL must be completed ≥ 14 days prior to registration with the following exceptions: intrathecal chemotherapy, hydroxyurea, corticosteroids, 6-mercaptopurine, methotrexate, vincristine, and/or leukapheresis to reduce circulating absolute lymphoblast count to ≤ 10,000/μL or prevent complications related to ALL are allowed but must be completed ≥ 24 hours prior to the initiation of protocol therapy.

Patients should have resolution of any acute non-hematologic toxicities of prior therapy to NCI CTCAE v5.0 grade ≤ 1.

Required Initial Lab Values:

- Peripheral blood absolute lymphoblast count ≤ 10,000/μL (treatment allowed as above to reduce blast count to ≤ 10,000/μL)

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