PATIENT ENROLLMENT PATHWAY
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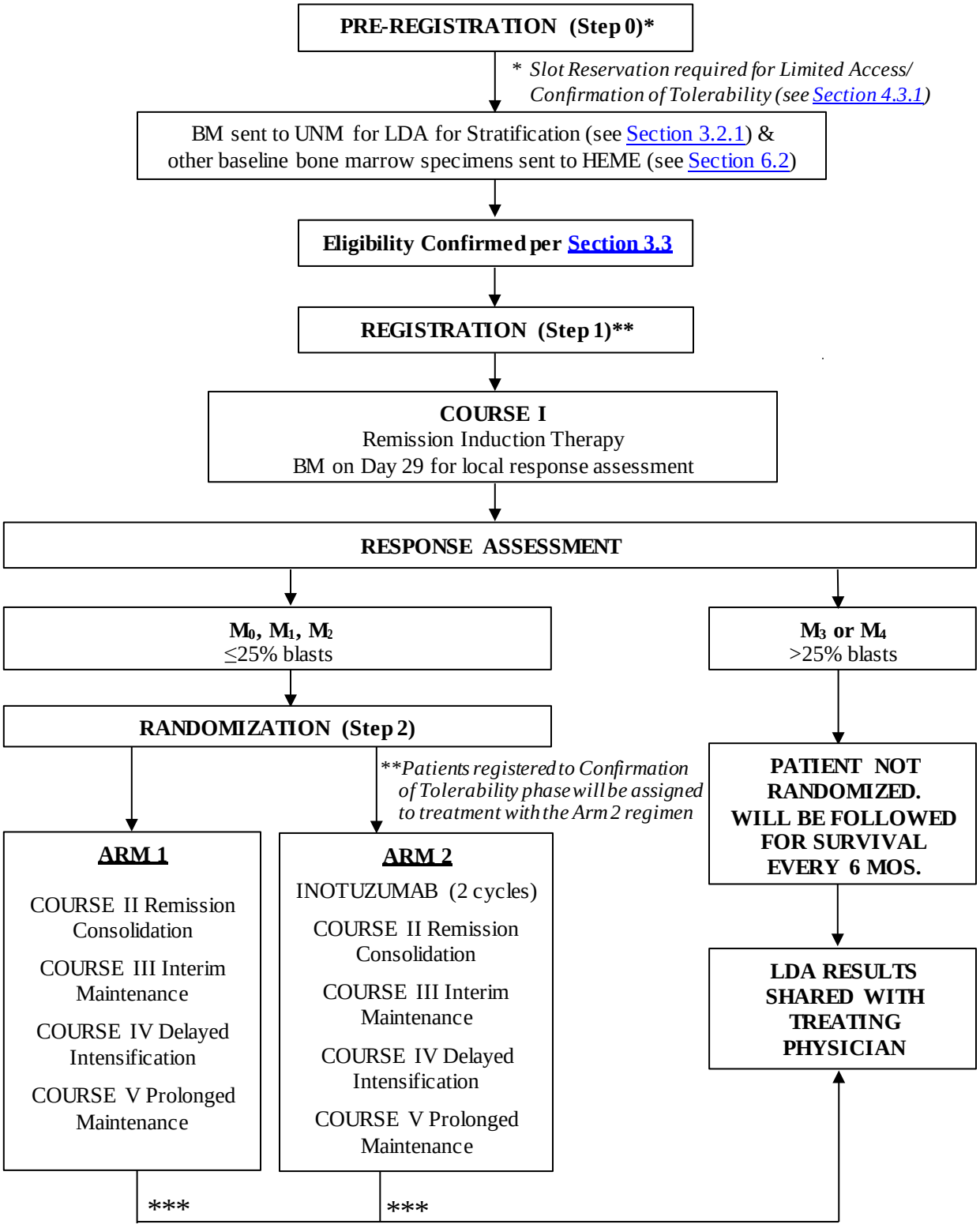

*** *If at any time a patient progresses or relapses on Arms 1 or 2, LDA results will be shared with the treating physician upon documentation of relapse or progression.*

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

Treatment courses are specified using a roman numeral, followed by a cardinal indicating the number of days from the start of that course (e.g., Day III-28 is the 28th day of Course III). See Section 7.1 for requirements prior to initiation of therapy and infection prophylaxis. If patient has consented to A041501-PP2, collect and submit specimens as required per Section 6.2.

Course I is to begin ≤ 5 days of registration (Step 1).

COURSE I: REMISSION INDUCTION THERAPY (see Section 7.2)

	Allopurinol until peripheral blasts and extramedullary disease are reduced ▯▯▯▯▯																			
	IT Ara-C																			
	Dex Days 1 – 7 ▯▯▯▯▯														Dex Days 15- 21					
	VCR							VCR							VCR			VCR		
	DNR							DNR							DNR			DNR		
				PEG ▯	▯	▯														
								IT MTX							(*)			(*)		IT MTX
																				BM
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	...	22	…	29

Allopurinol — Allopurinol 300 mg/day (unless allergic) to continue until peripheral blasts and extramedullary disease are reduced.

IT-Ara-C — Cytarabine 70 mg IT on Day 1. IT cytarabine may be given prior to registration for patient convenience at the time of diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Patients should remain in a horizontal position for at least 30 minutes following administration of intrathecal chemotherapy to enhance drug delivery to the head. If administered prior to study registration, systemic chemotherapy must begin within 72 hours of this intrathecal therapy.

Dex — Dexamethasone 5 mg/m^2 PO or IV BID on Days 1-7 and 15-21. Do not taper.

VCR — Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 1, 8, 15, and 22. Voriconazole and posaconazole are contraindicated with vincristine.

DNR — Daunorubicin 25 mg/m^2 IV on Days 1, 8, 15, and 22.

PEG — PEG-asparaginase 2000 IU/m^2 IV x 1 dose on Day 4 (OR Day 5 OR Day 6). **(cap dose at 3750 IU)** Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent) prior to PEG-asparaginase.

IT-MTX — Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) on Day 8 and Day 29.
(*) For patients with CNS3 disease, IT-MTX is also administered on Day 15 and 22.

BM — Bone marrow aspirate and biopsy specimen must be obtained on Day 29 to assess induction response and minimal residual disease (see Section 5.0 and 7.2.2).

RANDOMIZATION (see Section 4.4, 4.5 and 7.2.2):

Patients must meet eligibility in Section 3.4 in order to be randomized. Randomization must occur within 21 days after completion of remission induction therapy. Patients will be assigned to treatment Arms 1 or 2 according to the results of Day I-29 bone marrow. Patients who achieve M2 or better (M0, M1, M2) will be randomized to Arm 1(C10403 backbone) or Arm 2 (C10403 backbone with two 28-day cycles of inotuzumab (1.5 mg/m^2 per cycle unless found to not be sufficiently tolerable)). Patients who fail remission induction (M3 or M4) not be eligible for randomization, and the treating physician will be provided with LDA results. For patients who relapse at any time on Arms 1 or 2, LDA results will be provided to the treating physician.

Patients randomized to Arm 1 will go straight to Consolidation Course II (see Schema Page 5). Patients on Arm 1 SHOULD NOT receive inotuzumab. Patients randomized to Arm 2 will receive two 28-day cycles of inotuzumab (see Schema Page 4).

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

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ARM 2 INOTUZUMAB: ARM 2 ONLY (see Section 7.3)

ONLY PATIENTS ASSIGNED TO ARM 2 WILL RECEIVE INOTUZUMAB. Patients assigned to Arm 2 must begin inotuzumab within 7 days after peripheral blood counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL. If counts not recovered within 4 weeks, then contact the study chairs.

The Confirmation of Tolerability portion of the study has been completed. The phase III inotuzumab dose will be 0.5 mg/m^2/day on Days 1, 8, and 15 of a 28-day cycle (total dose per cycle is 1.5 mg/m^2/cycle).

Cycle 1

	INO							INO							INO	
																BM
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	28

INO Inotuzumab ozogamicin 0.5 mg/m^2/day IV on Day 1, 8 and 15 of a 28-day cycle. Total dose of inotuzumab is 1.5 mg/m^2/cycle. (Maximum of two cycles pending confirmation of tolerability). Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent). *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 7.3.*

BM Bone marrow aspirate and biopsy specimen must be obtained for all patients on Arm 2 on Day 28 of each cycle of inotuzumab to assess initial response and minimal residual disease.

Cycle 2

	INO							INO							INO	
																BM
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	28

INO Inotuzumab ozogamicin 0.5 mg/m^2/day IV on Day 1, 8 and 15 of a 28-day cycle. Total dose of inotuzumab is 1.5 mg/m^2/cycle. (Maximum of two cycles pending confirmation of tolerability). Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent). *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 7.3.*

BM Bone marrow aspirate and biopsy specimen must be obtained for all patients on Arm 2 on Day 28 of each cycle of inotuzumab to assess initial response and minimal residual disease.

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

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COURSE II: REMISSION CONSOLIDATION (see Section 7.4)

Begin Course II within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the study chairs. 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 should not be interrupted for myelosuppression alone except on Day 29. **Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL.** If patient has consented to A041501-PP2, collect and submit specimens as required per Section 6.2.

Patients with clinical evidence of testicular disease at diagnosis that does not resolve completely by the end of induction should receive radiation to testes during consolidation therapy (see Section 7.8.2).

	CTX													
	Ara-C Days 1 - 4							Ara-C Days 8 - 11						
	6-MP on Days 1-14													
	IT MTX							IT MTX						
	R							R						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14

	IT MTX*							IT MTX*						
	VCR							VCR						
	PEG													
Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28

***Day 15 and Day 22 IT MTX omitted for CNS3 patients.**

	CTX*													
	Ara-C* Days 29 - 32							Ara-C Days 36 - 39						
	6-MP on Days 29*- 42													
	R							R						
Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42

*** HOLD DAY 29 CHEMOTHERAPY UNTIL ANC ≥ 750/µL and platelets ≥ 75,000/µL.**

	VCR							VCR						
	PEG													
														BM
Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56

CTX Cyclophosphamide 1000 mg/m^2 IV on Day 1 and 29. See Section 7.4 for hydration instructions.

Ara-C Cytarabine 75 mg/m^2 IV or SC on Days 1-4, 8-11, 29-32, and 36-39.

6-MP 6-Mercaptopurine 60 mg/m^2 PO on Days 1-14 and 29-42. 6-MP is not to be taken with milk or citrus products. Give 6-MP at least one hour after the evening meal. 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/m^2/week. Round to the nearest 25 mg dose. Do not escalate dose based on blood counts during this course.

IT-MTX Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) on Days 1, 8, 15, and 22 **[omit dose on Day 15 and 22 for CNS3 patients]**. Patients should remain in a horizontal position for at least 30 minutes following administration of intrathecal chemotherapy to enhance drug delivery to the head. Send CSF for cell count and cytospin exam.

R **For CD20+ patients only (as defined in Section 3.3.2)**: Rituximab 375 mg/m^2 IV on Days 1 and 8 and then again on Days 29 and 36. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent).

VCR Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 15, 22, 43, and 50. Voriconazole and posaconazole are contraindicated with vincristine.

PEG PEG-Asparaginase 2000 IU/m^2 IV on Days 15 and 43. **(cap dose at 3750 IU)** Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent) prior to PEG-asparaginase.

BM Bone marrow aspirate and biopsy specimen must be obtained on Day 56 to assess induction response and minimal residual disease (see Section 7.4.2).

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

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COURSE III: INTERIM MAINTENANCE (Capizzi Methotrexate) (see Section 7.5)

Begin Course III within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the study chairs.

Therapy should be interrupted for patients with severe infections and resumed when the signs of the infection have abated. VCR and IV methotrexate should be held for 4 days if ANC < 500/µL or platelets < 50,000/µL on the planned treatment day (See Section 8.4.3).

If patient has consented to A041501-PP2, collect and submit specimens as required per Section 6.2.`

	VCR										VCR										VCR
	IV MTX										IV MTX										IV MTX
	R										R										
		PEG																			
	IT MTX																				
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

											VCR									VCR			
											IV MTX									IV MTX			
	PEG																						
											IT MTX												
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	...	49

VCR Vincristine 1.5 mg/m^2 (maximum 2 mg) IV push on Days 1, 11, 21, 31, and 41. Voriconazole and posaconazole are contraindicated with vincristine.

IV-MTX Methotrexate starting dose 100 mg/m^2 IV (escalate by 50 mg/m^2/dose) on Days 1, 11, 21, 31, and 41. If ANC > 750/µL and platelets > 75,000/µL, then escalate methotrexate dose by 50 mg/m^2 per dose (e.g., the Day 11 dose would be 150 mg/m^2). **Cap dose at 200 mg/m^2.** Obtain blood counts prior to each dose of methotrexate. **See Section 8.4.3 for methotrexate dose modifications for myelosupression.** Cotrimoxazole (sulfamethoxazole/trimethoprim) should not be given on the same day as methotrexate.

R **For CD20+ patients only (as defined in Section 3.3.2)**: Rituximab 375 mg/m^2 IV on Days 1 and 11. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent).

PEG PEG-Asparaginase 2000 IU/m^2 IV on Days 2 and 22. **Cap dose at 3750 IU.** Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone, and 25-50 mg diphenhydramine (or equivalent) prior to PEG-asparaginase.

IT-MTX Methotrexate 15 mg IT on Days 1 and 31. To enhance drug delivery to the head, patients should remain in a horizontal position for at least 30 minutes following administration of intrathecal chemotherapy. Send CSF for cell count and cytospin exam.

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

COURSE IV: DELAYED INTENSITIFICATION (see Section 7.6)

A bone marrow aspirate and biopsy must be obtained prior to initiation of Course IV.

Begin Course IV within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL.

If counts not recovered within 4 weeks, then contact the study chairs. Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting Delayed Intensification Therapy on Day 1 and again on Day 29. All therapy should be interrupted for patients with severe infections and should be resumed when the signs of the infection have abated. Otherwise, therapy should not be interrupted for simple myelosuppression.

	VCR							VCR							VCR						
	Dex Days 1-7														Dex Days 15-21						
	DOX							DOX							DOX						
	R							R													
				PEG																	
	IT MTX																				
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

								CTX*													
								Ara-C*							Ara-C						
								6-TG*													
								IT MTX*							IT MTX						
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42

*** Hold Day 29 chemotherapy until ANC > 750/µl and platelets > 75,000/µl.**

	VCR							VCR
	PEG							BM
Day	43	44	45	46	47	48	49	50

VCR Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Days 1, 8, 15, 43, and 50. Voriconazole and posaconazole are contraindicated with vincristine.

Dex Dexamethasone 5 mg/m^2 PO or IV BID on Days 1-7 and 15-21. Round to nearest 2 mg dose.

DOX Doxorubicin 25 mg/m^2 IV on Days 1, 8, and 15.

R **For CD20+ patients only (as defined in Section 3.3.2)**: Rituximab 375 mg/m^2 IV on Days 1 and 8. Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent).

PEG PEG-Asparaginase 2000 IU/m^2 IV on Day 4 (OR Day 5 OR Day 6) **AND Day 43. (cap dose at 3750 IU)** Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent) prior to PEG-asparaginase.

CTX Cyclophosphamide 1000 mg/m^2 IV on Day 29. See Section 7.6 for hydration instructions.

Ara-C Cytarabine 75 mg/m^2 IV or SC on Days 29-32 and 36-39.

6-TG Thioguanine 60 mg/m^2/day PO on Days 29-42, at least 1 hour after the evening meal. 6TG is to be taken without milk or citrus products. Adjust dose using 40 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2.

IT-MTX Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) on Days 1, 29, and 36. To enhance drug delivery to the head, patients should remain in a horizontal position for at least 30 minutes following administration of intrathecal chemotherapy.

BM Bone marrow aspirate and biopsy specimen must be obtained for all patients approximately one week after completion of Course IV to assess remission status.

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

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COURSE V: MAINTENANCE THERAPY (12 week courses) (Section 7.7)

Patients must begin Course V within 7 days after peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. If counts not recovered within 4 weeks, then contact the study chairs.

Bone marrow examinations will be obtained every six months (prior to starting the first, third, fifth, etc., Maintenance Therapy courses), with a final exam within 1 month after the end of all planned therapy (See Section 5.0, 6.2 and 7.7.3).

All CNS3 patients who achieve a CR will receive cranial radiation therapy during the first cycle of Maintenance Therapy (see Section 7.8.1).

If patient consented to A041501-HO1 at pre-registration, the patient should be approached to confirm their consent to participate in the study during Maintenance Therapy as outlined in Section 6.3. Administer MEMs Caps and questionnaires per Section 6.3.

See next page for Course V treatment schema.

PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

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Repeat Maintenance Therapy courses (12 week courses; 84 day cycles) until total duration of therapy is 2 years from start of Interim Maintenance Therapy for female patients, or 3 years for male patients (see Section 7.7). Only mercaptopurine and methotrexate will be interrupted for myelosuppression.

	VCR																			
	Dex Days 1 - 5																			
	6-MP on Days 1-84																			
	IT MTX																			
								PO MTX							PO MTX						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

								VCR													
								Dex Days 29 – 33													
	6-MP on Days 1-84																				
								IT MTX*													
	PO MTX							PO MTX†							PO MTX						
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42

* IT MTX is given on Day 29 of the first 4 courses of maintenance therapy.
† PO MTX is held on Day 29 of the first 4 courses of maintenance therapy.

															VCR						
															Dex Days 57-61						
	6-MP on Days 1-84																				
	PO MTX							PO MTX							PO MTX						
Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63

	6-MP on Days 1-84																				
	PO MTX							PO MTX							PO MTX						
Day	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84

VCR — Vincristine 1.5 mg/m^2 (maximum dose 2 mg) IV on Days 1, 29, and 57. Voriconazole and posaconazole are contraindicated with vincristine.

Dex — Dexamethasone 6 mg/m^2/day PO or IV divided BID every 4 weeks on Days 1-5, 29-33, and 57-61. Round to the nearest 2 mg dose.

6-MP — 6-Mercaptopurine 75 mg/m^2/day PO on Days 1-84. 6-MP is to be taken at least one hour after the evening meal, and should not be taken with milk or citrus products. Adjust dose using 50 mg tablets, and different doses on alternating days in order to attain a weekly cumulative dose as close as possible to 525 mg/m^2/week. See Appendix II for details. See Section 8.4.5 for 6-MP dose escalation instructions.

IT-MTX — Methotrexate 15 mg IT (addition of 50 mg of hydrocortisone optional per institutional guidelines) on Day 1. **IT methotrexate also is given on Day 29 of the first 4 courses of maintenance therapy.** Patients should remain in a horizontal position for at least 30 minutes following the administration of intrathecal chemotherapy to enhance drug delivery to the head.

PO-MTX — Methotrexate 20 mg/m^2 PO weekly on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. Round to nearest 2.5 mg dose. **PO methotrexate is held on Day 29 of the first 4 courses of maintenance therapy (when IT methotrexate is given).** See Section 8.4.5 for dose escalation instructions. If patient is receiving prophylaxis with cotrimaxazole (sulfamethoxazole/trimethoprim), do not give on the same day as methotrexate administration.

3.0 PATIENT SELECTION

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

3.1 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 infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with known HIV infection are eligible if they meet all of the following criteria in addition to the other protocol eligibility criteria:
    - No history of AIDS-related complications other than a history of low CD4+ T-cell count (<200/mm^3) 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.
    - Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the leukemia.
    - Serum HIV viral load of < 200 copies/mm^3 on combination antiretroviral therapy with minimal pharmacokinetic interactions with study therapy and minimal overlapping clinical toxicity with protocol therapy.
        - Recommend a regimen of the integrase inhibitor dolutegravir combined with either disoproxil fumarate/emtricitabine or dolutegravir combined with tenofovir alafenamide/emtricitabine protease inhibitors
        - Once daily formulations containing cobicistat not allowed owing to potential pharmacokinetic interactions with leukemia therapy.
        - Stavudine and zidovudine not allowed because of overlapping toxicity with protocol therapy.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agents.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control 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).

3.2 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.

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

___ **3.2.1 Bone marrow submission for LDA Assay**

Submission of bone marrow aspirate for LDA assay is mandatory prior to registration for stratification. It should be initiated as soon as possible after pre-registration. The specimen should be sent to the University of New Mexico lab as outlined in Section 6.2.2.

Please note: Bone marrow aspirate and peripheral blood should also be submitted at this time for central MRD analysis and FISH as outlined in Section 6.2.3.

3.3 Registration Eligibility Criteria (Step 1)

___ **3.3.2 Documentation of Disease:**

___ • Newly diagnosed patients with CD-22 positive B-cell acute lymphoblastic leukemia (WHO criteria) are eligible. Patients with Burkitt type ALL are NOT eligible.

___ • Patients who have BCR-ABL fusion transcript determined by FISH or RT-PCR or t(9;22)(q34;q11) by cytogenetics are not eligible and should be considered for enrollment on studies that incorporate imatinib during induction.

Please note: Patients must also be assessed for CD20 positivity and other markers as outlined in Section 5.0.

Positivity for CD22 and CD20 is defined as baseline expression of the CD22 or CD20 antigen in more than 20% of leukemic cells using local multiparameter flow-cytometric immunophenotyping with the use of CD45 expression as a marker to gate the ALL blast population, according to recommendations from the European LeukemiaNet.

___ **3.3.3 Prior Treatment**

___ • No prior therapy for ALL except for limited treatment (≤ 7 days) with corticosteroids or hydroxyurea and a single dose of intrathecal cytarabine. However, patients who are being treated with chronic steroids for other reasons (for example, to treat asthma, autoimmune disorders, lupus, etc.) are eligible.

___ • No prior therapy for acute leukemia except emergency therapy (corticosteroids or hydroxyurea) for blast cell crisis, superior vena cava syndrome, or renal failure due to leukemic infiltration of the kidneys. When indicated, leukapheresis or exchange transfusion is recommended to reduce the WBC.

___ • Single-dose intrathecal cytarabine is allowed prior to registration or prior to initiation of systematic therapy for patient convenience. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a

second lumbar puncture. Systemic chemotherapy must begin within 72 hours of this intrathecal therapy.

___ **3.3.4 Not pregnant and not nursing**, because this study involves agents that have known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 8 days prior to registration is required.

___ **3.3.5 Age ≥ 18 years and < 40 years.**

___ **3.3.6 ECOG Performance Status 0-2**

___ **3.3.7 Patients with Down Syndrome are excluded from this study** due to the likelihood of excessive toxicity resulting. These patients should be treated in consultation with a pediatric oncologist.

___ **3.3.8 Lab Values**

AST, ALT	≤ 3 x upper limit of normal (ULN), unless suspected leukemic involvement of the liver
Direct Bilirubin	≤ 3 x upper limit of normal (ULN), unless suspected leukemic involvement of the liver
Calc. Creatinine Clearance	≥ 50 mL/min by Cockcroft-Gault

3.4 Randomization Eligibility Criteria (Step 2)

___ **3.4.1 Completion of remission induction therapy (per Section 7.2).**

___ **3.4.2 Patients with M2 marrow or better (see table below) are eligible.** Patients with M3 or M4 marrow (greater than 25% lymphoblasts) will not be eligible to be randomized.

Rating	Blast Cells (%)*
M_0	0 – 5.0
M_1	0 – 5.0
M_2	5.1 – 25.0
M_3	>25.0 – 50.0
M_4	> 50.0

* The term "blast cell" includes any cell that cannot be classified as a more mature normal element, and includes "leukemic cells," pathologic lymphocytes, and stem cells.

___ **3.4.3 Lab Values**

Absolute Neutrophil Count (ANC)	≥ 750/mm^3
Platelet Count	≥ 75,000/mm^3
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN), except for patients with known Gilbert's syndrome
AST	≤ 8 x upper limit of normal (ULN)