

SWOG S1318: A Phase II Study of Blinatumomab (NSC-765986) and POMP (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) for Patients \geq 65 Years of Age with Newly Diagnosed Philadelphia-Chromosome Negative (Ph-) Acute Lymphoblastic Leukemia (ALL) and of Dasatinib (NSC-732517), Prednisone and Blinatumomab for Patients \geq 65 Years of Age with Newly Diagnosed Philadelphia-Chromosome Positive (Ph+) ALL.

Fast Facts

Cohort 2 is not available to CRCWM

Registration Step 1 – Induction/Re-Induction

Disease Related Criteria

1. Patients must have a new morphologic diagnosis of precursor B cell acute lymphoblastic leukemia (ALL) (non T cell) based on WHO criteria as defined in Section 4.1b. Patients with Burkitts (L3) are excluded. Patients with Ph-positive or Ph-like ALL with dasatinib-sensitive mutations or kinase fusions may have relapsed or refractory diagnoses.
2. Patients must have a diagnosis of Philadelphia chromosome negative ALL or Ph chromosome positive ALL by cytogenetics, FISH or polymerase chain reaction (PCR). Patients will be registered to receive treatment in either Cohort 1 (ph-) or Cohort 2 (Ph+) based on these results. Diagnostic specimens must be submitted to the site's local CLIA-approved cytogenetics laboratory and results of tests (cytogenetics, FISH or PCR) must confirm Ph status prior to registration. If not already known, BCR-ABL status (p190 or p210) must be evaluated in Ph-positive patients by PCR.

For Cohort 2, Ph-like testing is not required specifically for this study. However, to be registered to Cohort 2 under the Ph-like DSMKF criterion, the patient must have a known or presumed activating Ph-like signature and dasatinib-sensitive mutation or kinase fusion, such as: ABL1, ABL2, CSF1R, PDGFRB, PDGFRA, or FGFRs that was otherwise identified as part of normal standard of care. Prior to registering any patients with a known or presumed activating Ph-like signature and dasatinib-sensitive mutations or kinase fusions (DSMKF) treating physicians must confirm eligibility with the study chairs via email to S1318SC@swog.org. The study chairs must respond via email with confirmation of patient eligibility prior to patient registration.

3. Patients must have evidence of ALL in their marrow or peripheral blood with at least 20% lymphoblasts present in blood or bone marrow collected within 14 days prior to registration.

For ALL in marrow or peripheral blood, immunophenotyping of the blood or marrow lymphoblasts must be performed to determine lineage (B cell, T cell or mixed B/T cell). Appropriate marker studies including CD19 (B cell), must be performed. Co-expression of myeloid antigens (CD13 and CD33) will not exclude patients. If possible, the lineage specific markers (myeloid cells) should be determined. The blood/bone marrow sample for these assays must be obtained within 14 days prior to registration.

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Patients with only extramedullary disease in the absence of bone marrow or blood involvement are not eligible.

Clinical/Laboratory Criteria

1. 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, active ALL in the CNS confirmed by CSF analysis, or other significant CNS abnormalities.
2. Patients must have a lumbar puncture to determine CNS involvement of ALL within 14 days prior to registration. Categories of CNS involvement are outlined in Section 18.6. Patients with CNS3 are excluded from the trial; patients with CNS1 or CNS2 will be eligible, but will be monitored for CNS involvement. Note that intrathecal methotrexate administered during the pre-study lumbar puncture may count as the first dose of intrathecal therapy required as part of the study (see Section 7.1a).

Cohort 1, Ph- Patients only:

3. Patients must not have received any prior chemotherapy, radiation therapy, or other therapy for the treatment of ALL (other than those noted below) and must not be receiving any immunosuppressive therapy. Patients may not have received any prior investigational therapy within 28 days prior to registration. Patients may have received the following within any time prior to registration: low dose chemotherapy, TKI therapy, steroids, hydroxyurea, leukapheresis, intrathecal chemotherapy or vincristine. Patients must not have received any monoclonal antibody therapy within 42 days of registration. NOTE: The allowance of the listed prestudy therapies is to reduce the blast count to < 50,000 in order to minimize the risk of tumor lysis syndrome.
4. In the event that the patient's bone marrow blast count is $\geq 50\%$ blasts, patients may be registered but should receive steroids for 3-5 days in order to reduce tumor burden prior to blinatumomab administration, as follows.
 - a. Prephase treatment with dexamethasone (10-20 mg/m²) for 3-5 days is required for patients with bone marrow blasts $\geq 50\%$, peripheral blood blasts 15,000/uL or higher, or elevated LDH suggesting rapidly progressive disease per investigator opinion.
 - i. Pre-treatment should conclude at least 24 hours prior to the first dose of blinatumomab (although additional dexamethasone is automatically given as a pre-med prior to the first dose). At the time of first infusion of blinatumomab, the absolute peripheral blast count should be < 25,000/uL.
 - ii. Note: For the purposes of the study, Day 1 of the cycle will be the first day of blinatumomab administration.
5. It is preferred, but not required, that corticosteroids and hydroxyurea should start only after all diagnostic samples have been obtained. However, if the patient was previously on corticosteroids and/or hydroxyurea, this is allowable provided that the patient still has measurable disease at time of the bone marrow aspirate.
 - a. Corticosteroids and/or hydroxyurea, as well as any of the other therapies mentioned (with the exception of IV cyclophosphamide), may continue to be administered, at physician discretion, until 1 day prior to blinatumomab administration.
 - b. IV cyclophosphamide must be discontinued at least 7 days prior to blinatumomab administration.

Cohort 2, Ph+ and Ph – like DSMKF patients only:

6. Patients must NOT have received a prior autologous or allogeneic hematopoietic stem cell transplant at any time. Patients must NOT have received any chemotherapy, investigational agents, or undergone major surgery within 14 days prior to registration, with the following exceptions:
 - a. Monoclonal antibodies must not have been received for 1 week prior to registration.
 - b. Chimeric antigen receptor (CAR) T-cells must not have been received for 28 days prior to registration.
 - c. Steroids, hydroxyurea, vincristine, 6-mercaptopurine, methotrexate, thioguanine and intrathecal chemotherapy are permitted within any timeframe prior to registration. FDA-approved TKIs may also be administered until 1 day prior to start of study therapy (C1, D1). IV cyclophosphamide may be administered at doses of 1 g/m² or less until up to 7 days prior to registration.

7. Patients must be ≥ 65 years of age. For patients 65-69 years of age, patient must be deemed not suitable for standard intensive Induction chemotherapy at the discretion of the local investigator, or must have refused standard intensive chemotherapy.

Cohort 1, Ph- Patients only:

8. Patients must not be candidates for allogeneic hematopoietic stem cell transplant. NOTE: Subjects up to age 70 years who are considered fit for allogeneic hematopoietic stem cell transplant, should be considered for enrollment on E1910, in order to avoid competing with that study. If a patient is considered unfit for intensive chemotherapy at the time of initial diagnosis, but subsequently achieves a CR, then it will be left to the treating physician's discretion to consider HSCT.
9. Patients must have complete history and physical examination within 28 days prior to registration.
10. Patients must have a Zubrod Performance Status of 0-2 (see Section 10.0).
11. Patients must have serum creatinine ≤ 1.5 mg/dl within 14 days prior to registration.
12. Patients must have AST and ALT ≤ 3.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.
13. Patients must have total bilirubin ≤ 2.0 x IULN within 14 days prior to registration.
14. Patients must have alkaline phosphatase ≤ 2.5 x IULN within 14 days prior to registration.
15. Patients must not have systemic fungal, bacterial, viral or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
16. Patients must not have CTCAE \geq Grade 2 neuropathy (cranial, motor or sensory) within 14 days prior to registration.
17. Patients known to be positive for HIV (the human immunodeficiency virus) may be eligible, providing they meet the following additional criteria within 28 days prior to registration:
 - No history of AIDS-defining conditions
 - CD4 cells > 350 cells/mm³
 - If on antiretroviral agents, must not include zidovudine or stavudine
 - Viral load ≤ 50 copies HIV mRNA/mm³ if on cART or $\leq 25,000$ copies HIV mRNA/mm³ if not on cART.
 - HAART regimens are acceptable providing they have only weak P450A4 interactions.
18. Patients must not have any known autoimmune disease.
19. Patients must not have testicular involvement. If clinical or ultrasound findings are equivocal, biopsy must be performed. All tests for establishing testicular involvement must be completed within 14 days prior to registration.
20. Patients with evidence of extramedullary disease at diagnosis will have CT scan or MRI of the chest, abdomen and pelvis to obtain baseline values within 28 days prior to registration. See Section 7.1b for additional CT/MRI time points during treatment.
21. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated 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 five years.
22. Patients must have the following tests within 28 days prior to registration to obtain baseline measurements:
 - PT/PTT/INR/fibrinogen

Cohort 1, Ph- patients only

- Neurologic assessment (see Section 7.1c.2)

Cohort 2, Ph+ and Ph – like DSMKF patients only:

Patients must not have active pericardial effusion, ascites or pleural effusion of any grade based on chest x-ray and echocardiogram within 28 days prior to registration. Exception: If the effusion is suspected to be related to the leukemia, the patient may have pericardial effusion \leq Grade 2 or pleural effusion \leq Grade 1.

Cohort 2, Ph+ and Ph – like DSMKF patients only:

Patients must have ejection fraction \geq 45% based on echocardiogram performed within 28 days prior to registration.

Cohort 2, Ph+ and Ph – like DSMKF patients only:

Patients must have QTcF (by Fridericia calculation) $<$ 480/msec based on EKG performed within 28 days prior to registration.

- $QTcF = QT/(RR)0.33$
- (QTcF = QT interval divided by the cube root of the RR [heart rate] in seconds)

Cohort 2, Ph+ and Ph – like DSMKF patients only:

Patients must not be receiving any proton pump inhibitors at the time of registration.

Specimen Submission Criteria

1. Pretreatment cytogenetics must be performed on all patients. Collection of pretreatment specimens must be completed up to 28 days prior to registration to S1318. Specimens must be submitted to the site's preferred CLIA-approved cytogenetics laboratory. BCR-ABL status must be verified in Ph-positive patients by FISH, cytogenetics, and/or PCR prior to enrollment. If a patient is Ph-positive, PCR for both p190 and p210 must be sent.
2. Patients must be offered participation in specimen submission for future research. With patient's consent, specimens must be submitted as outlined in Section 15.3.
3. Cohort 1 (Ph-negative patients only): Patients must have specimens submitted for blinatumomab immunogenicity assessment. Collection of pretreatment specimens must be completed up to 28 days prior to registration to S1318. Specimens must be submitted to LabConnect as outlined in Section 15.2.
4. Cohort 2 (Ph-positive and Ph- like DSMKF patients only): Patients must agree to have specimens submitted for blinatumomab immunogenicity testing if subsequently moved to a blinatumomab containing treatment regimen on protocol.

Registration Step 2 – Post-Remission Therapy

1. Cohort 1 (Ph-negative patients only): Patients must have achieved CR or CRi within 2 cycles of Induction/Re-Induction with blinatumomab.
2. Cohort 2 (Ph-positive and Ph-like DSMKF patients only): Newly diagnosed Ph+, Newly-diagnosed Ph-like DSMKF, and relapsed/refractory Ph+ patients without prior dasatinib or other 2nd or 3rd generation TKI therapy, must have achieved CR or CRi within 1 cycle of Induction with dasatinib/prednisone, or within 2 cycles of Re-Induction with blinatumomab. Relapsed/refractory Ph+ or Ph-like DSMKF patients with prior dasatinib or other 2nd or 3rd generation TKI therapy must have achieved CR or CRi within 2 cycles of Re-Induction therapy with blinatumomab.
NOTE: Day 1 of Post-Remission = Day 43 of the preceding cycle (+/- 3 days)
3. Patients must have serum creatinine \leq 1.5 mg/dl within 14 days prior to registration.
4. Patients must have AST and ALT \leq 3.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.

5. Patients must have total bilirubin $\leq 2.0 \times$ IULN within 14 days prior to registration.
6. Patients must have adequate marrow function as evidenced by ANC $\geq 750/\text{mcl}$ and platelets $\geq 50,000/\text{mcl}$ within 28 days prior to registration.
7. Patients must be registered to Step 2 within 28 days after count recovery. (Note: there is no maximum allotted time period for count recovery, providing patient remains in CR or CRi.)
8. All non-hematologic treatment related toxicities that are deemed clinically significant by the treating investigator must have resolved to \leq Grade 2.

Registration Step 3 – Maintenance

1. Patients must have documented CR or CRi within 28 days prior to registration. Note that bone marrow examination is only required if there are clinical signs/symptoms of progression. If progression is a concern due to the length of the time for count recovery, a bone marrow examination is recommended.
2. Patients must have serum creatinine $\leq 1.5 \text{ mg/dl}$ within 14 days prior to registration.
3. Patients must have AST and ALT $\leq 3.0 \times$ Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.
4. Patients must have total bilirubin < 2.0 within 14 days prior to registration.
5. Patients must have adequate marrow function as evidenced by ANC $\geq 750/\text{mcl}$ and platelets $\geq 75,000/\text{mcl}$ within 28 days prior to registration.
6. All non-hematologic treatment related toxicities that are deemed clinically significant by the treating investigator must have resolved to \leq Grade 2.

Pre-Study Parameters

- History & Physical
- CBC/diff/platelets, CMP,
- PT/PTT/INR
- Bone Marrow Aspirate & Biopsy
- Biopsy for testicular involvement
- Lumbar Puncture
- FISH and/or PCR
- Neurologic Assessment
- CD4/Viral Load
- Chest X-Ray, CT or MRI, ECHO, and EKG